From the Department of Molecular Medicine and Surgery
Karolinska Institutet, Stockholm, Sweden

ONCOLOGICAL SAFETY AND HEALTH-RELATED QUALITY OF LIFE AFTER RECONSTRUCTIVE BREAST CANCER SURGERY

Hannah Coudé Adam

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ONCOLOGICAL SAFETY AND HEALTH-RELATED QUALITY OF LIFE AFTER RECONSTRUCTIVE BREAST CANCER SURGERY

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By

Hannah Coudé Adam

Principal Supervisor:
Jana de Boniface, M.D, associate professor
Karolinska Institutet
Department of
Molecular Medicine and Surgery

Co-supervisors:
Jan Frisell, M.D, professor
Karolinska Institutet
Department of
Molecular Medicine and Surgery

Ann-Charlott Docherty Skogh, M.D, PhD
Karolinska Institutet
Department of
Clinical Science and Education

Opponent:
Miss Fiona MacNeill, M.D, FRCS
Royal Marden NHS Hospital Trust
London, UK

Examination Board:
Christian Ingvar, M.D, senior professor
Lunds University
Department of
Clinical Sciences, Lund

Jenny Bergqvist, M.D, associate professor
Karolinska Institutet
Department of Oncology and Pathology

Birgit Stark, M.D, associate professor
Karolinska Institutet
Department of
Molecular Medicine and Surgery

To Jacquie…

ABSTRACT

The main aim of this thesis was to gain knowledge about the oncological safety of nipple-sparing mastectomy (NSM) with immediate implant-based reconstruction and delayed Deep Inferior Epigastric Perforator (DIEP) flap breast reconstruction. In this context, we also considered the impact of discrepancies in socioeconomic status (SES) and comorbidity. Finally, we investigated the effects of radiotherapy (RT) on implant-based immediate breast reconstruction (IBR) measuring failure rates, number of unplanned reoperations and patient-reported outcomes (PROs).

In **study I**, we studied the local recurrence rates as well as disease-free, overall and breast cancer-specific survival (BCSS) after NSM and IBR compared with a matched control group of patients undergoing conventional mastectomy. Matching variables were tumour stage, age, and year of mastectomy. A total of 69 NSM cases and 206 conventional mastectomies operated between 2000 and 2012 were included. While no local recurrence occurred in the study group, seven were observed in the control group (P=0.197). Survival rates did not differ significantly between groups.

In **study II**, we aimed to estimate the risk of breast cancer recurrence after DIEP flap reconstruction compared with patients treated with mastectomy without any delayed reconstruction. A total of 254 DIEP cases operated between 1999 and 2013 and 729 control cases were included. Matching variables were age, tumour stage, neoadjuvant therapy, and year of DIEP flap reconstruction. The primary endpoint, 5-year BCSS, was significantly higher in the DIEP group, which did not persist after adjustment for tumour and patient characteristics and treatment. Overall survival (OS) remained significantly lower in the control group despite adjustment. We therefore aimed to address the observed survival differences by further adjusting for SES) and comorbidity in **study III**. Data for the estimation of the Charlson Comorbidity Index and SES were obtained from Swedish national registers. In the DIEP group, it was more common to continue education after primary school, to have a higher income, and to be in a partnership. Women in the DIEP group were also significantly healthier than women in the control group. After adjustment for SES and comorbidity, however, OS was still significantly better in the DIEP group than the control group, which is potentially due to unaccounted confounders such as body mass index (BMI), smoking and selection bias inherent to the reconstructive decision-making process.

In **study IV** we re-evaluated a previously reported large homogenous IBR cohort with regards to surgical results and PROs. All women undergoing a therapeutic mastectomy with implant-based IBR at Stockholm's main four hospitals between 2007 and 2011 were included (N=754 IBRs). Of those, 386 had not been irradiated, 64 were irradiated prior to IBR, and 304 after IBR. The primary endpoint was IBR failure, defined as implant removal due to any cause, with or without a conversion to an autologous reconstruction. BREAST-Q questionnaires were sent out to all patients alive with no record of implant removal. Between-group comparisons and longitudinal within-groups differences were assessed. IBR failure occurred in 128 cases (17%) with the higher proportion in the postoperative and prior RT groups, 24.3% and 31.3% respectively, ($P<0.001$). Independent risk factors for IBR failure were irradiation, age > 50 at time of IBR, BMI ≥ 25, and postoperative surgical complication. With a response rate of 72.2%, women with prior RT scored significantly lower than those without RT on most subscales, while women with postoperative RT reported significantly lower scores on physical well-being only. Among responders, psychosocial well-being had increased over the past eight years in the postoperative RT group, and satisfaction with breasts and with overall outcome had significantly decreased in the no RT group. Of note, women with implant failure after irradiation were not included in PROs analysis since the specific questions are not applicable to someone who has either had her implant removed or converted to an autologous reconstruction. Thereby, PROs results may have been affected by selection bias.

LIST OF SCIENTIFIC PAPERS

I. The oncological safety of nipple-sparing mastectomy
-A Swedish matched cohort study.
H. Adam, M. Bygdeson, J. de Boniface.
European Journal of Surgical Oncology, 40:1209-1215, 2014.

II. Risk of recurrence and death in patients with breast cancer after delayed deep inferior epigastric perforator flap reconstruction**.**
H. Adam, A. C. Docherty Skogh, Å. Edsander Nord, I. Schultz, J. Gahm, P. Hall, J. Frisell, M. Halle, J. de Boniface.
British Journal of Surgery 105:1435-1445, 2018.

III. Breast cancer patients with a delayed DIEP flap breast reconstruction have a higher socioeconomic status, less comorbidity and better survival
H. Coudé Adam, A. C. Docherty Skogh, Å. Edsander Nord, I. Schultz, J. Gahm, P. Hall, J. Frisell, M. Halle, J. de Boniface.
Submitted.

IV. Radiotherapy in implant-based immediate breast reconstruction: long-term surgical outcomes and patient-reported outcome measures in a Swedish multicenter cohort.
H. Coudé Adam, A. Frisell, Y. Liu, H. Ikonomidis Sackey, I. Oikonomou, A. C. Docherty Skogh, J. Frisell, J. de Boniface.
In manuscript.

CONTENTS

LIST OF ABBREVIATIONS

AI	Aromatase inhibitor
AJCC	American Joint Committee on Cancer
ASCO	American Society of Clinical Oncology
BCS	Breast-conserving surgery
BCSS	Breast cancer-specific survival
BMI	Body mass index
CAP	College of American Pathologists
CI	Confidence interval
CCI	Charlson Comorbidity Index
CT	Computed tomography
CTCs	Circulating tumour cells
DCIS	Ductal carcinoma in situ
DFS	Disease-free survival
DIEP	Deep inferior epigastric perforator flap
EBCTCG	Early Breast Cancer Trialists' Collaborative Group
ER	Estrogen receptor
ER+	Estrogen receptor positive
EUSOMA	European Society of Breast Cancer Specialists
HER2	Human epidermal growth factor receptor 2
HR	Hazard ratio
HRQoL	Health-related quality of life
IBR	Immediate breast reconstruction
ICD-10	International Classification of Diseases-10th Revision
IHC	Immunohistochemistry
INCA	Informationsnätverk för cancervården
IoT	Register on Income and Taxes
LISA	Longitudinal Integration Database for Health Insurance and Labour Market Studies
LR	Local recurrence
LRR	Locoregional recurrence
LRFS	Local recurrence-free survival
MRI	Magnetic resonance imaging

NAC	Nipple-areola complex
NACT	Neoadjuvant chemotherapy
NHG	Nottingham histological grade
NKBC	National Quality Register for Breast Cancer
NPR	National Patient Register
NSM	Nipple-sparing mastectomy
OS	Overall survival
pCR	Pathological complete remission
PgR	Progesterone receptor
PMRT	Post-mastectomy radiotherapy
PNR	Personal identity number
PROs	Patient-reported outcomes
RCC	Regional cancer centre
RCT	Randomized controlled trial
RR	Regional recurrence
RT	Radiotherapy
SES	Socioeconomic status
SERM	Selective oestrogen receptor modulators
SSM	Skin-sparing mastectomy
TDLU	Terminal duct lobular units
TNBC	Triple-negative breast cancer
TND	Tumour-nipple distance
TNM	TNM Classification of Malignant Tumors
TPR	Total Population Register
TRAM	Transverse rectus abdominis myocutaneous
U.S	The United States
WBI	Whole breast irradiation
WHO	World Health Organization

1 BACKGROUND

Breast cancer is the most frequently diagnosed cancer in women of all regions of the world, representing 22% (1.38 million) of all cancer cases worldwide[1,2]. It accounts for approximately 14% (523 000 cases were diagnosed in 2018) of all malignancies in Europe, making it one of the leading causes of cancer-related death, accounting for 22% (138 000) of cancer deaths in European women in 2018[1]. The incidence in developed countries is 80 cases per 100 000 women but <40 cases per 100 000 women in developing countries where the incidence is rising, possibly due to improving diagnostics and a more "western-like" lifestyle. In Sweden, about 8400 women were diagnosed with breast cancer in 2012, 8093 in 2017, 7952 in 2018, and 8288 in 2019[3]. Figure 1a-b presents the incidence and mortality in Sweden since the 1960s, with an age-standardized incidence rate now reaching 84.7 per 100 000 female individuals[4]. Due to screening, early-stage presentation is most common; in the United States (U.S) for example, about 61% of women present with localized breast cancer and only 32% have regional lymph node involvement[5]. Survival rates have been increasing in western countries during the past decades, commonly attributed to mammography screening and advances in oncological treatment, along with increasing breast cancer awareness and improving general healthcare[6].

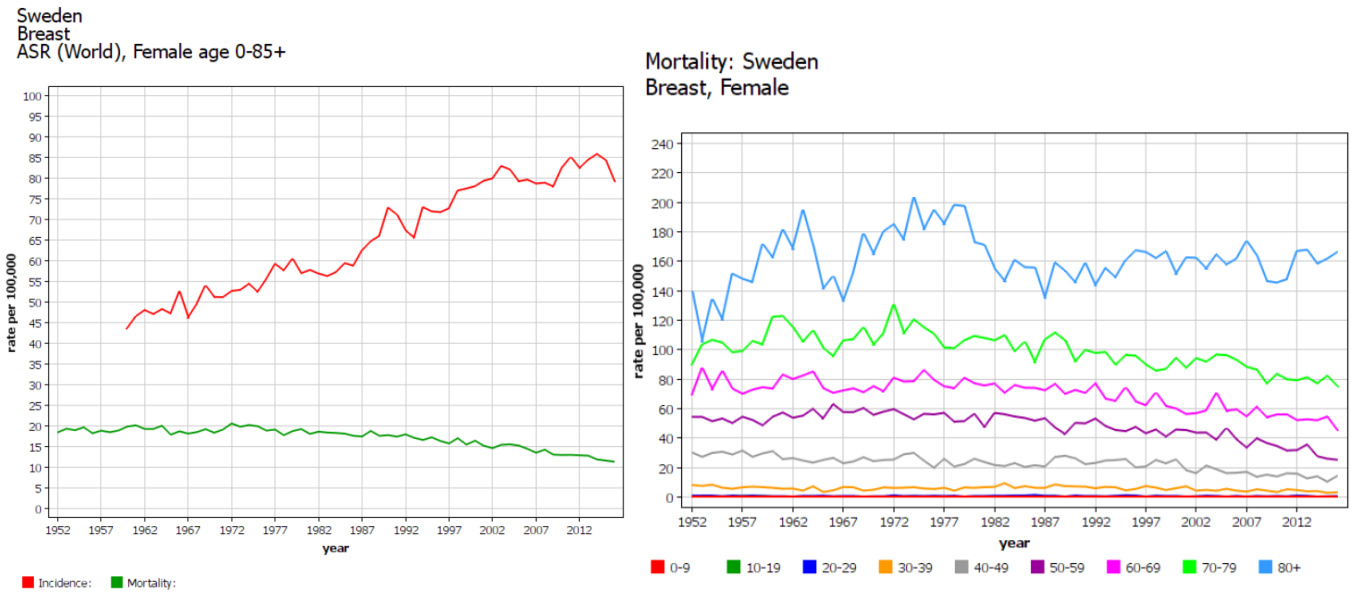


Figure 1a. (left) presenting the age-standardized breast cancer incidence in Sweden per 100 000 women (red curve) and breast cancer mortality (green curve) **1b**. (right) Breast cancer mortality per age category. Curves obtained from NORDCAN[4]

Breast cancer is diagnosed by triple assessment including clinical examination, radiological assessment with mammography and/or ultrasound, and pathological confirmation by either fine-needle aspiration cytology or core needle biopsy. The triple assessment has a sensitivity of almost 100%[7] and if any doubts remain thereafter, magnetic resonance imaging (MRI) or a diagnostic surgical biopsy may be helpful[8]. Mammography screening was first introduced in Sweden in 1986 and was thereafter implemented nationally. Today, all women between the age of 40 and 74 years are invited to mammography screening with the interval of 24 months, according to guidelines by The Swedish National Board of Health and Welfare[9].

The management of breast cancer requires a multidisciplinary approach in both diagnostics and treatment. According to Swedish guidelines, each patient should be discussed at pre- and postoperative multidisciplinary meetings as established more than 25 years ago, bringing together a breast surgeon, breast radiologist, breast oncologist, pathologist, and a breast nurse. Based on the team discussion of the results including tumour and nodal stage, tumour type, any genetic predisposition, tumour biology, and other patient characteristics such as age and comorbidity, a treatment recommendation is given[10].

1.1 TUMOUR CLASSIFICATION, PROGNOSTIC AND TREATMENT-PREDICTIVE FACTORS

1.1.1 TNM classification

The TNM staging system is developed by the American Joint Committee on Cancer (AJCC)[11]. Its classification is based on tumour size (T), regional lymph node metastasis (N) and distant metastasis (M), and represents the single most important prognostic factor in breast cancer[12]. The TNM system classifies breast cancer into four stages with close associations to survival. The 5-year overall survival (OS) in stage 0-I disease is nearly 100%, approximately 80% in stage II, 60% in stadium III, but barely 20% in stage IV[8]. The overall 5-year survival rate in Sweden has increased over the past decade, now approaching 83%[3].

TNM stage is defined at different time points during the cancer treatment: The clinical or radiological assessment before the initiation of tumour treatment defines clinical stage, whereas pathological stage is based on the histopathological examination of surgically removed tissue. If the latter is undertaken after preoperative systemic treatment, the TNM classification is clearly marked with a “y” to avoid incorrect staging.

1.1.2 Histological Grade

Histological grade is a strong prognostic factor, first described in 1957[13] and later modified by Elston and Ellis in 1991[14]. The overall grade is based on three morphological features of the cancer cells including tubular formation, nuclear atypia and mitotic count, each of which creates a score that is added together to an overall grade of I-III, today referred to as the Nottingham histological grade (NHG).

1.1.3 Biomarkers

Routinely assessed biomarkers include Oestrogen receptor (ER), Progesterone receptor (PgR), human epidermal growth factor receptor 2 (HER2), and the proliferation marker Ki67[15]. These biomarkers provide both prognostic and treatment-predictive information. ER was first identified in the 1970s through the association with a beneficial tumour response after endocrine ablation[16]. The receptor is expressed in up to 80-85% of invasive breast tumours, offering a target for endocrine therapy.

PgR expression is dependent on oestrogen signalling via ER[17], and its prognostic value has been disputed[18,19]. Still, tumours expressing PgR are associated with better outcomes than PgR-negative tumours[20-22]. The threshold for ER and PgR positivity, earlier set to 10%, was updated in recommendations by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) in 2010, and tumours expressing ER or PgR in at least 1% of the tumour nuclei are since considered positive[23,24]. A follow-up study including 9639 cases, however, showed no strong additional benefit of endocrine therapy in tumours with 1-9% of ER positivity[25,26] and therefore, a threshold of 10% is incorporated in the Swedish guidelines[8].

Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor located on the cell membrane, overexpressed in about 10-15% of all breast cancers[24,27,28]. It is involved in a signalling network controlling cellular proliferation, associated with the capacity of metastatic dissemination leading to more aggressive tumour traits, and is correlated to worse overall survival[29,30]. HER2 is primarily assessed by immunohistochemistry (IHC) and subsequently completed by situ hybridization if amplification is suspected[8].

Ki67 is a nuclear protein expressed only in proliferating cells, reflecting the tumour proliferation rate, and reported as a value between 0 and 100% representing the proportion of proliferating tumour cells. There are still debates on a standardized cut-off value to distinguish between high, intermediate and low proliferative tumours[24,25,31,32]. The proliferation index is

determined through Ki67 or MIB-1, which are monoclonal antibodies directed against the Ki67 protein.

A prognostic factor is defined as a factor that provides information about recurrence or survival independently of treatment effects. Information about such factors can be useful in the selection of patients for a certain treatment, but does not predict the response to the treatment[33]. A predictive factor, on the contrary, provides information on the effect of a therapeutic intervention in a patient, and thus an estimate for the response to treatment[34]. Predictive biomarkers can be specifically targeted by therapy[33] and guide the selection of treatment strategies, e.g. ER positivity for endocrine therapy and HER2 positivity for targeted immunotherapy. Thus, hormone receptor status, HER2 status and histological grade act as determinants for the type of adjuvant systemic therapy recommended[34]. A high proliferation rate, although an independent prognostic factor, is not predictive of benefit from chemotherapy or endocrine treatment[35].

1.1.4 Molecular subtypes

Breast cancer comprises a heterogeneous group of tumours with distinct molecular features. The classification of intrinsic molecular subtypes was first described by Perou and Sørlie et al in 1999[36,37]: Four subtypes of different gene expression patterns were identified and termed luminal, HER2-enriched, basal-like, and normal-breast like. Further luminal subtyping followed with the distinction between luminal A and luminal B[38]. Molecular subtypes have been translated into corresponding surrogate subtypes as determined by the expression of hormone receptors, HER2 and proliferation markers[39,40]. Today, surrogate intrinsic subtypes are five: *luminal A* (ER and PgR positive, HER2 negative, low proliferative activity), *luminal B* (ER and PgR positive, high proliferative activity, HER2 negative), *HER2-positive luminal* (ER and PgR positive, HER2 positive), *HER2-positive non-luminal* (ER and PgR negative, HER2 positive), and *triple-negative breast cancer (TNBC)* (ER and PgR negative, HER2 negative; see Figure 2)[38,41,42].

The clinical importance of breast cancer subtypes has been widely reported[11,43,44] and incorporated into the St. Gallen clinical guidelines in 2011[25,41]. This subtype classification is crucial to decide systemic treatment plans for breast cancer patients[11].

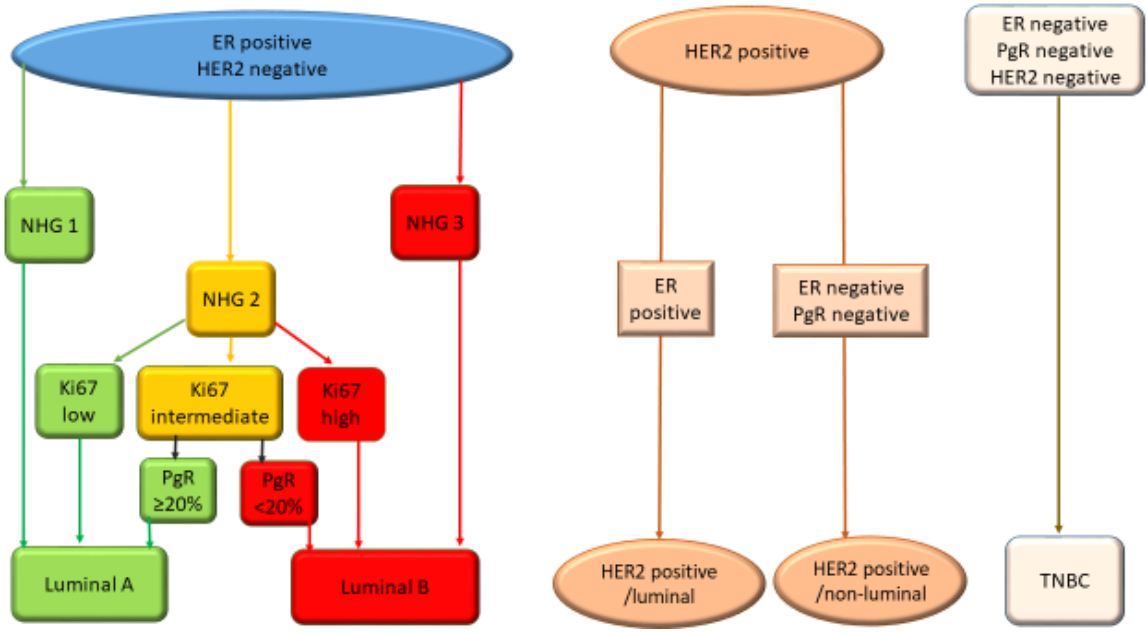


Figure 2. Flow chart presenting the surrogate intrinsic subtype classification according to the Swedish guidelines. ER-positivity defined as ER ≥10% whereas laboratory-specific cut-offs are used for Ki67 proliferation. Presented according to the 2020 Swedish guidelines for breast cancer treatment[8].

1.2 BREAST CANCER TREATMENT

Breast cancer treatment is multimodal with both locoregional and systemic treatment approaches. Systemic therapy is given with the aim to eliminate residual locoregional as well as systemic micrometastatic disease, thereby lowering the risk of breast cancer recurrence[45]. Neoadjuvant, i.e. preoperative, systemic treatment can be chosen with the aim to down-stage the primary tumour and allow for less extensive surgery in the breast and axilla. Locoregional treatment modalities are surgery and radiotherapy: while surgery focuses on eliminating the macroscopic tumour burden, radiotherapy eradicates microscopic residual disease.

1.2.1 Surgery

The modern history of breast cancer treatment dates back to 1882, when William Halsted performed the first radical mastectomy removing the whole breast together with the underlying pectoralis major and minor muscles and the ipsilateral axillary lymph nodes[46,47]. The procedure was associated with disfigurement and severe morbidity including persistent pain, sensory loss, severe lymphedema, and restricted shoulder mobility[47]. Since then, major improvements have evolved, resulting in more conservative approaches in both breast and axillary surgery. In the breast, the most common surgical alternatives are breast-conserving surgery (BCS) and mastectomy (today leaving the pectoral muscles untouched). In the axilla, more precise staging methods such as the sentinel lymph node biopsy have in many situations replaced full axillary lymph node dissection (previously always part of a radical mastectomy), and thus spare patients the heavy comorbidity seen with previous approaches. Surgical tumour resection remains the primary component of breast cancer treatment and may in many cases be curative without further therapy.

BCS is the surgical removal of the tumour with an appropriate margin of healthy surrounding tissue and is, in combination with radiotherapy, the golden standard in women with early-stage breast cancer[48]. About 68% of all breast cancer patients in Sweden receive BCS[10]. In tumours up to three cm, the proportion is as high as 83%[8]. However, mastectomy may be necessary due to large tumour size, multifocality, centrally situated tumours, patient preference, or inflammatory breast cancer[10]. It implies the removal of the entire breast gland, with or without the overlying skin.

1.2.2 Radiotherapy

Although breast cancer surgery removes macroscopic disease, undiagnosed microscopic tumour foci may be left behind in residual breast tissue, lymph nodes or lymph tracts resulting in locoregional recurrence (LRR) or distant metastasis if left untreated[49,50]. Postoperative radiotherapy (RT) is recommended in order to eradicate microscopic residual disease, thereby reducing the risk of LRR and improving breast cancer-specific survival (BCSS) both in the setting of BCS[50] and mastectomy in node-positive disease[49,51,52]. Local RT targets the remaining breast tissue, overlying skin and underlying chest wall after BCS (whole breast irradiation, WBI) or the skin and chest wall after mastectomy (post-mastectomy radiotherapy, PMRT), while locoregional RT additionally targets draining lymphatics in the axilla and supra- and infraclavicular fields, and the internal mammary chain in selected cases.

For indication and target delineation of postoperative RT, information on axillary lymph node status, tumour size and surgical method is crucial[8,10]. National guidelines today recommend RT delivered as two tangential fields in 15 fractions, resulting in a total dose of 40 Gray. An additional boost dose of 10-16 Gray is given to patients younger than 50 years[10].

According to recommendations by the European Society of Breast Cancer Specialists (EUSOMA), RT should be considered if the risk of local recurrence (LR) following breast surgery is estimated to be at least 20% at 10 years after diagnosis[52]. This has been incorporated into the Swedish and European guidelines, recommending WBI to patients undergoing BCS[8,53]. WBI can be omitted in cases of pure in situ disease of NHG 1-2 if the total extent does not exceed 15 mm and if clear margins are achieved (>2 mm)[8]. Investigations by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) suggest a reduced 10-year recurrence risk from 35% to 19.3% (CI 13.7–17.7, P<0.00001) in those receiving WBI after BCS[50]. Furthermore, breast cancer mortality 15 years after diagnosis is reduced from 25.2% to 21.4% (P=0.00005)[50].

In node-positive breast cancer, RT to regional lymph nodes is recommended in Sweden independent of the type of breast surgery performed, and is always combined with local RT, i.e.WBI after BCS or PMRT after mastectomy: After mastectomy, the risk of breast cancer recurrence as well as breast cancer mortality in women with node-positive disease is reduced if RT is given[49,51,54]. In a meta-analysis by the EBCTCG, including 13132 patients, locoregional RT reduced breast cancer recurrence (RR=0.86, 95% CI 0.79–0.94, P=0.0006), breast cancer mortality (RR=0.81, 0.74–0.90, p<0.0001) and overall mortality (RR=0.86, 0.80–0.93, P=0.0002) in all nodal stages[54]. If only axillary micrometastases are present, however, and in patients with only a single macrometastasis and favourable tumour biology (i.e. luminal A),

local RT after BCS (WBI) is deemed sufficient, and no RT is recommended after mastectomy[8]. PMRT can be further omitted in pure in situ tumours of limited extent and in case of lymph node negativity in T1-T2 stage tumours excised with clear margins[10]. PMRT is, however, recommended if the tumour size exceeds 5 cm regardless of nodal stage or if extensive multifocality is present[8].

In a meta-analysis including 8135 women, locoregional RT reduced the locoregional ($P<0.00001$) and overall recurrence risk ($P=0.0003$) and breast cancer mortality ($P=0.04$) in women with four or more positive lymph nodes undergoing mastectomy, independent of systemic therapy[51]. In another systematic review and meta-analysis, RT was shown to significantly reduce the risk of LRR even in case of one to three positive lymph nodes[55]. A beneficial but limited effect was also seen on OS. In many countries, however, the role of locoregional RT in patients with early-stage T1–2 disease with limited nodal metastasis, i.e. one to three positive lymph nodes, remains a subject of debate[56]. In these cases, RT could be omitted in patients lacking specific risk factors for LRR, i.e. patients over the age of 40 with clinical stage I-II, unifocal tumours of luminal A subtype with clear surgical margins, and additionally in those achieving pathological complete remission in the breast and lymph nodes after preoperative systemic therapy[57,58].

1.2.3 Chemotherapy

Chemotherapy has been part of breast cancer treatment since the 1960s[59]. In a meta-analysis by the EBCTCG including data on 100 000 women, a combination of 5-flurouracil, epirubicin and cyclophosphamide resulted in a 16% reduction of recurrence and 21% reduction of mortality compared with no cytotoxic treatment[60]. More recent regimens include taxanes either following anthracycline-based treatment or alone[61], routinely used for high-risk tumours such as triple-negative or HER2-positive breast cancer[34,53].

Adjuvant chemotherapy prolongs recurrence-free and breast cancer-specific survival[22,61]. It is not clear, however, whether it completely eradicates or only reduces the size of occult distant tumour foci[34]. Adjuvant chemotherapy has been suggested to benefit almost all groups of breast cancer patients, although not necessarily to the same degree[22]. Chemotherapy is, however, associated with significant adverse side effects, some of which are temporary and relatively easily managed while others are more serious and long-lasting, including severe toxicities that may lead to treatment-associated mortality[62]. Some suggest that patients with an estimated recurrence risk higher than 10% over the course of 10 years should be considered potential candidates for chemotherapy[63]. According to Swedish guidelines, chemotherapy is recommended on the base of the combination of a number of risk factors such as high grade and/or high proliferation, TNBC and HER2-positive subtypes, lymph node positivity, and young age[8].

Neoadjuvant chemotherapy (NACT) was originally only indicated in locally advanced or inflammatory breast cancer. Today, however, it is used in an increasing number of patients with aggressive tumour biology. NACT helps to monitor treatment response, thus allowing treatment adaptation if response is lacking, and increases the likelihood for breast-conserving surgery[10,34,64-66]. The proportion of tumours responding to neoadjuvant chemotherapy varies dependent on tumour subtype[65,67-71], and pathological complete response (pCR) positively correlates with better breast cancer-specific survival[72].

In Sweden, 9.0% of breast cancer patients were treated with NACT in 2019[3], which is low in comparison to other countries. A survey addressing international multidisciplinary teams showed that the proportion of all breast cancer patients receiving NACT in Australia, Germany, Italy, the United Kingdom, and the U.S ranged between 7 and 27%[73].

1.2.4 Endocrine therapy

Approximately 80-85% of breast cancers are oestrogen receptor positive (ER+), in which case adjuvant endocrine therapy is recommended[8,53,74]. Endocrine treatment reduces endogen hormone activity either by blocking hormone receptors through competitive linkage or by inhibition of the precursor conversion to bioactive stages: Selective oestrogen receptor modulators (so-called SERMs) such as Tamoxifen have anti-estrogenic properties by competing with oestrogen in target tissues[75,76]. SERMs are most often used in premenopausal and low-risk postmenopausal women. Aromatase inhibitors (AI) such as anastrozole are inhibitors of the aromatase enzyme, resulting in a diminished oestrogen production, most often used in medium to high-risk postmenopausal women[77].

An absolute reduction of breast cancer mortality by 9.2% during the first 15 years post treatment (relative risk: 0.71 during years 0-4, 0.66 during years 5-9 and 0.68 during years 10-14) has been shown for ER+ patients after five years of Tamoxifen treatment[18]. In another meta-analysis by the EBCTCG on 32 000 ER-positive tumours in postmenopausal women comparing the effects of AI and Tamoxifen, the relative risk of recurrence was lowered by 30% for those treated with AI. A decrease of breast cancer mortality (RR 0.86, $P<0.001$) was in favour of AI[78]. Importantly, however, EBCTCG reported late breast cancer recurrences throughout a follow-up of 5-20 years after five years of adjuvant endocrine therapy in 2017; risk factors associated with late distant recurrences were large tumour size and advanced axillary status. Prolonged endocrine therapy lasting for 10-15 years is therefore recommended in selected patients[79].

The addition of bisphosphonates to endocrine treatment inhibits osteoclast-mediated bone resorption and thereby reduces the risk of distant metastases[80]. A significantly lower 10-year risk for distant metastasis was seen in patients treated with adjuvant bisphosphonates versus controls (20.4% vs 21.8%, $P=0.03$)[81], and the 10-year risk of bone metastasis was 7.8% versus 9.0% ($P=0.004$) leading to a significantly reduced breast cancer mortality in the treatment group. Bisphosphonates may also improve health-related quality of life (HRQoL) in cancer patients with bone metastases by reducing bone pain[82].

1.2.5 Anti-HER2 targeted therapy

Before the humanized anti-HER2 targeted monoclonal antibody trastuzumab (Herceptin®) was introduced, HER2-positive tumours carried a dismal prognosis[34]. After several large randomized controlled trials (RCT), trastuzumab was added to the standard chemotherapy regimen, improving the prognosis for patients with HER2-positive tumours considerably[83,84]: A meta-analysis concluded a 40% reduction in the proportional risk of recurrence along with 34% relative improvement in overall survival (HR 0.66: 95%CI 0.57-0.77)[85]. Today, patients with HER2-positive tumours larger than 5 mm are offered anti-HER2 treatment regardless of age or menopausal status[8,53,86]. In the neoadjuvant setting, a combination of the HER2 antibodies trastuzumab and pertuzumab ("double blockade") is given, resulting in significantly higher rates of pCR along with an improved superior disease-free survival (DFS)[87-90].

1.3 BREAST RECONSTRUCTION

Around 36% of all breast cancer patients in the U.S underwent mastectomy year 2011[91] and the corresponding figure in Sweden was 32% in 2019[8]. In conventional mastectomy, the breast glandular tissue is removed together with the overlying skin and the nipple-areola complex (NAC). The procedure is associated with negative psychological effects resulting in reduced self-esteem, changed body image and impaired sexual function[92]. Further development of conventional mastectomy techniques led to skin preservation, which results in better aesthetic outcomes and allows an improved breast shape in the reconstructed breast[93]: In skin-sparing mastectomy (SSM), at least parts of the native skin envelope are preserved for an immediate breast reconstruction (IBR), and in nipple-sparing mastectomy (NSM), also the nipple-areola complex (NAC) is preserved.

Following mastectomy, breast reconstruction can be performed as an immediate or delayed procedure, each of which can be done using a breast implant or autologous tissue to recreate the breast mound, or a combination of both. The goal of post-mastectomy breast reconstruction is to restore the appearance of the breast and thereby mitigate the psychological impact of cancer surgery[94-98]. The choice of reconstruction method is multifactorial and based on tumour characteristics, the reconstructive setting (immediate or delayed), body habitus, any pre-existing comorbidity, patient preference and patient-received information. All patients planned for mastectomy are recommended to receive preoperative information about available reconstruction methods, and those wishing IBR without any significant contraindication should be offered one[99].

The rates of IBR have been steadily increasing over the past decade[100-103]. Implant-based reconstructions account for almost 65% of all breast reconstructions in the U.S. and are considered safe, cost-effective and reliable[104-107]. Since implant-based IBR is the least demanding reconstructive method, it can be performed despite limited comorbid conditions[108]. Contraindications for IBR include inflammatory cancer, tumour-growth into the skin or the chest wall, simultaneous distant metastasis, smoking and obesity. Although no clear cut-off has been explicitly set, a body mass index (BMI) above 30 is regarded as contraindication for breast reconstruction in Sweden[8].

1.3.1 Immediate breast reconstruction

The first silicone breast implant was introduced in the 1960s and evolved into a tissue expander which was used from the 1990s onwards[109,110]. Since then, implants have developed to vary in material (hydrogel-filled or different cohesivity versus saline-filled expanders/implants), surface texture (smooth versus textured silicone implants), design (variable volume or fixed volume), and shape (anatomical versus round)[111,112].

In Sweden, implant-based reconstruction is the predominant method in the setting of IBR, performed in about 16% of women undergoing mastectomy nationwide, but in 32% in the Stockholm region in year 2019[3]. The proportion of breast cancer patients undergoing implant-based IBR in Sweden, even though still low in an international comparison, has steadily been increasing since 2000[3]. Autologous reconstruction methods are more commonly chosen in a delayed setting in Sweden, but commonly performed as an immediate breast reconstruction in other countries[113-116].

Implant-based reconstruction can either be performed with the implants placed in a subpectoral pocket or in the prepectoral space, with or without the additional use of acellular dermal matrix or synthetic mesh, and further performed as a one-stage direct-to-implant reconstruction or in a two-stage setting, first placing an expander implant which is later replaced by a definitive implant. In one-stage reconstruction, permanent implants are used in order to reconstruct a definitive breast mound at the time of mastectomy, without the need for tissue expansion and tissue expander to implant exchange[104]. Some state that women with small-to-medium and non-ptotic breasts are best suited for the procedure[117]. No significant delay in the time to adjuvant radiotherapy or other oncological treatment has been proven in patients undergoing implant-based IBR[118,119].

1.3.2 Nipple-sparing mastectomy

Immediate breast reconstruction implies that larger parts of the native skin envelope need to be preserved, necessitating specific types of mastectomy such as skin-sparing mastectomy (SSM) or nipple-sparing mastectomy (NSM) in order to achieve a superior cosmetic outcome[48]. The preservation of the nipple-areola complex (NAC) in NSM results in higher psychological satisfaction among women[120] and NSM may help to optimize the contour of the breast[121].

Figure 3. Non-irradiated patient with bilateral nipple-sparing therapeutic mastectomy and implant-based immediate breast reconstruction. The left breast holds a permanent, partly saline-filled expander, while the right breast holds a permanent implant after expander exchange. Photo: Jana de Boniface.

Some doubts have been raised about the oncological safety of NSM since breast tissue such as terminal ducts could be left behind in the preserved NAC and potentially lead to recurrence[122,123]. Terminal duct lobular units (TDLU) constitute the basic functional and histopathological unit of the breast. TDLU consist of intra- and extralobular terminal ducts with an associated lobe and range in size from 1 to 4 mm. The units connect to ducts of each breast lobe, draining through collecting ducts terminating in the nipple. Although residual breast tissue can be found throughout the whole area of the chest wall, breast tissue could more often be left behind on the skin flaps after conventional mastectomy, at the periphery of the breast mound if more technically challenging accesses are used, or underneath the NAC[124]. Some researchers show that up to 76.2% of conventional mastectomy specimens contain breast tissue at the resection margins across the superficial dissection surface[124-126].

NAC involvement, i.e. occult tumour involvement of the nipple-areola complex, may lead to incomplete excision of the tumour. The incidence of NAC involvement ranges from 0% to 58%, most probably dependent on criteria for patient selection and pathologic assessment[127-131]. Several studies have reported an increased risk of NAC involvement in large tumours in the vicinity of the NAC, in centrally located tumours, high-grade tumours, tumours with

positive axillary lymph nodes, an extensive in situ component, and lymphovascular invasion[132-135]. Another factor increasing the risk of NAC involvement is a short tumour-nipple distance (TND)[136,137]. Consequently, one of the established criteria for attempting NSM is a TND of at least 1-2 cm as judged by clinical examination and imagining. The only absolute contraindication for NSM remains clinical NAC involvement, while relative contraindications include a short TND and locally advanced disease. In order to confirm that the NAC can be left in place in NSM, a retroareolar biopsy should always be examined to assure that no NAC involvement is present.

The risk of local recurrence following NSM or SSM in the context of IBR has been widely investigated and a selection of these studies is presented in Table 1[93,134,136,138-153].

Author (year)	*Number of cases*	*Tumour stage*	*Local recurrence rate (%)*	*NAC recurrence rate (%)*	*Median follow-up (months)*
Gerber (2009)	61	0-III	11.7	1.6	101*
Petit (2008)	579	0-I	0.9	0	19
Benediktsson (2008)	216	0-III	24.0	-	156
Paepke (2009)	109	0-III	0.9	0	34
Coopey (2013)	315	0-III	2.6	0	22*
Smith (2017)	311	0-III	2.2	0	51
Poruk (2015)	130	0-IV	0.8	-	25.8
Frey (2016)	118	0-III	0.8	0	30.7
Margenthaler (2020)	399	0-III	1.0	0	Not reported
Adam (2014)	69	I-IV	0	0	36

* Mean follow-up time

Table 1. A selection of studies reporting on the local recurrence following nipple-sparing or skin-sparing mastectomy.

A systematic review of 13 studies found 144 recurrences in 2015 patients undergoing NSM. Conclusions were, however, hard to draw due to lack of adjusting for potential confounding factors such as adjuvant radiotherapy, age, surgical techniques, stage of disease, ductal carcinoma in situ or invasive breast cancer, and chemotherapy in many of the studies[154]. Another meta-analysis and systematic review of 20 studies presented factors associated with OS, disease-free survival (DFS) and local recurrence (LR), supporting the safe use of NSM[155].

In a recent systematic review comparing NSM to SSM, no statistically significant difference in 5-year DFS and mortality was shown, and LR rates were similar (3.9 vs 3.3 %, P=0.45)[156].

Based on the data presented above, NSM is considered to be an oncologically safe choice in carefully selected women[53,139,149,155,156].

1.3.3 The effects of radiotherapy on implant-based immediate breast reconstruction

The proportion of IBR patients receiving post-mastectomy radiotherapy (PMRT) has increased over time[91,157]. Analyses of trends for studies reported to the U.S. National Cancer Database showed an increase in the proportion of women with an IBR receiving PMRT from 13% to 33% between 2004 and 2013[103,158]. PMRT has a negative impact on the cosmetic outcome after implant-based IBR and is linked to higher rates of surgical complications including postoperative infection, wound dehiscence, seroma, and skin flap necrosis[58,159-163].

While the formation of a capsule surrounding the breast implant is physiological and due to the inflammatory response to a foreign object, the late complications of capsular contracture refers to the fibrosis of the capsule, commonly induced by radiation and often associated with pain, impaired cosmetic outcome, lack of softness, and implant migration[105,164-167]. These effects may lead to psychological distress and impaired HRQoL[167]. The risk of capsule contracture is increased with bacterial contamination of the implant, type of implant and smoking. Capsular contracture occurs in approximately 20.0-40.4% following immediate and 17.0%-26.4% following delayed implant-based breast reconstruction[168,169].

Figure 4. Postoperatively irradiated patient with implant-based IBR to the left breast.
Photo: Jana de Boniface

Irradiation in the context of implant-based IBR increases surgical revisions and implant failure, defined as implant loss with or without secondary autologous reconstruction[163,165,166,170-173]. A meta-analysis including 1105 women undergoing implant-based breast reconstruction showed a 4.2 times higher risk of surgical complications in women receiving radiotherapy[166]. Implant failure affects 11-37% of irradiated patients[167,174-178]. Some authors question whether offering IBR to patients planned for PMRT is ethically correct[179], while it is internationally agreed that PMRT is no absolute contraindication for IBR in a well-informed patient[99]. From the patient's own perspective, implant failure implies negative effects on HRQoL related to reoperation, pain and repeated hospital visits, loss of income, sick leave, re-admission to surgery for implant removal and probably a subsequent or later conversion to an autologous reconstruction with a new risk of postoperative complications, sick leave and recovery period. With this in mind, even though Eriksson et al reported on lower satisfaction with the overall outcomes after IBR among irradiated patients, still 77.7% of patients receiving PMRT after IBR and not suffering implant failure would recommend it to other women in the same situation[175].

1.3.4 Delayed breast reconstruction

1.3.4.1 DIEP flap reconstruction

Delayed breast reconstruction may be performed using implants or autologous tissue or a combination of both. It is also possible to convert an immediate breast reconstruction to a delayed autologous reconstruction at a later time in case of complications, patient preference, or unsatisfactory aesthetic results. In Sweden, delayed autologous breast reconstruction is recommended to be performed no earlier than two years after initial breast cancer surgery with the rationale that half of breast cancer recurrences will have occurred by then[180,181]. For the included study population in this thesis, autologous breast reconstruction was primarily offered to irradiated patients[180]. One of the most common methods of delayed autologous breast reconstruction in Sweden today is the deep inferior epigastric perforator (DIEP) flap.

Breast reconstruction with perforator flaps started in the early 1970s with the knowledge that flaps of an increasing length-to-width ratio could be elevated safely[183,184]. This was soon followed by the development of the "free flap" technique, i.e. the free transfer of a non-pedicled tissue flap to the recipient site by microvascular anastomosis between perforator vessel stumps on the flap and adequate recipient vessels[185,186]. The transverse rectus abdominis myocutaneous (TRAM) flap was first introduced as a pedicled flap, and transfers one entire rectus abdominal muscle with an overlaying skin island; this, however, was often associated with donor site

complications including motor weakness, bulging, hernia, or weakness of the abdominal wall[187]. Therefore, the free TRAM flap was developed, using only of a limited piece of rectus abdominal muscle[188,189]. A further development of the method was the DIEP flap, first described in the U.S. in 1994 by Allen and Treece[190].

The DIEP flap is the adipose tissue and skin from the lower abdomen which is transposed to the mastectomy site as a free microsurgical transplant in order to rebuild the breast. In 1999, the method was described by Blondeel et al in Belgium who further popularized this technique[191]. The first DIEP flap reconstruction in Sweden was performed shortly thereafter and is today the first choice for free flap breast reconstruction with about 150-200 DIEP flap reconstructions per year.

Figure 5. Patient operated with right deep inferior epigastric perforator flap reconstruction. Preoperative photograph (left side) and one-year postoperative result (right side).
Photo:Ann-Charlott Docherty Skogh

Major surgery can be classified as severe physical trauma since it exposes large wound surfaces and has been hypothesised to cause tumour progression in breast cancer patients[192,193]. Delayed breast reconstruction may thus increase the risk of breast cancer recurrence through reactivation of dormant micrometastases. Previous results are contradictory as study groups of heterogeneous reconstructive methods have been included, and most studies lacking any

matched control groups[194-198]. In a publication by Isern et al, tumour stage was not taken into account and the number of DIEP flaps was limited; furthermore, the rate of lymph node metastasis was significantly higher for the cases than the controls (66.4 versus 53.8%)[197]. Other studies could not find any increased risk of recurrence after autologous breast reconstruction[194-196,199,200].

A summary of the studies investigating the risk of recurrence after autologous flap reconstruction are presented in Table 2[194,195,197-203]. Only two of these, however, exclusively include women with a DIEP flap reconstruction[202,203].

Author (year)	*Number of cases*	*Tumour stage*	*Recurrence proportions (%)*	*Control group*	*p-value*	*Median follow-up(months)*
Ross (2000)	92	0-III	5.4% (local recurrence)	None	-	36.7
Snoj (2006)	156	I-III	18.6% (any recurrence)	None	-	66
Isern (2011)	125	I-III	32.8% (any recurrence)	Mastectomy alone 20.9% (any recurrence)	Not reported	146
Lindford (2013)	112	I-IV	12.5% (distant recurrence)	Mastectomy alone 21.5% (distant recurrence)	**0.034**	102
Dillekås (2016)	312	I-IV	12.5% (any recurrence)	Mastectomy alone 3.8% (any recurrence)	0.08	137
Wu (2016)	397	0-IV	2.8% (local recurrence)	None	-	43
Svee (2018)	225	I-III	12.9% (any recurrence)	Mastectomy alone 15.1 % (any recurrence)	0.433	125
Geers (2018)	485	Not reported	8% (distant recurrence)	Mastectomy alone, 15% (distant recurrence)	**0.032**	68
Adam (2018)	*254*	*0-III*	*19.7% (any recurrence)*	*Mastectomy alone 23.9 % (any recurrence)*	*0.171*	*89*

Table 2. A selection of studies investigating breast cancer recurrence after autologous flap reconstruction

In Sweden, absolute contraindications for DIEP flap reconstruction are a BMI >30, active smoking and concomitant tumour recurrence or distant metastasis[180,181]. Relative contraindications include previous scars, e.g. after caesarean section or abdominoplasty casting doubt upon the integrity of perforators for the DIEP, diabetes, and cardiorespiratory comorbidities increasing surgical and on-table anaesthetic risk. Since year 2008, all patients planned for a DIEP flap reconstruction in Stockholm undergo screening for distant metastasis by contrast-enhanced chest and abdomen computed tomography (CT) scan. Preoperative CT angiography scan is further performed before the DIEP flap reconstruction in order to assure the existence and location of the perforating vessels arising from the deep inferior epigastric artery.

1.4 BREAST CANCER RECURRENCE

As metastatic disease is the major cause of breast cancer mortality, the primary aim of local and systemic therapy is to eradicate all active disease[204,205]. The shed of malignant cells into the circulation may potentially cause recurrence up to 20 years after surgical treatment[205]. Breast cancer is known for its propensity of late recurrences[206,207], and tumour cells can disseminate from early epithelial alterations as well as from carcinoma in situ[208]. Asymptomatic circulating tumour cells (CTCs) are found in the blood of breast cancer patients without any signs of recurrences up to 22 years after initial diagnosis[206]. This contributes to breast cancer being viewed as a systemic disease, and once the disease has metastasized, it is considered incurable[34]. The vast majority of breast cancer-related deaths occur due to metastatic tumour growth impairing the function of vital organs[34].

1.4.1 Local and regional recurrence

Local recurrence (LR) is defined as a recurrent tumour in the ipsilateral breast, be it at the original tumour site, ipsilateral skin or chest wall, often but not always carrying the same histopathologic features as the primary tumour. A recurrence in the ipsi- or contralateral axillary, infra- or supraclavicular, interpectoral or internal mammary lymph nodes is considered a regional recurrence (RR).

Approximately 20-30% of patients with early-stage breast cancer experience recurrent disease despite advances in early detection and comprehensive treatments[209,210]. Recurrence rates vary depending on the stage of the disease, the subtype and treatment[49,53,211-213]. A meta-analysis from the EBCTCG suggests that breast cancer recurs at a steady rate throughout a period of 5 to 20 years after diagnosis[79]. Still, approximately 80% of recurrences occur within the first two to five years after primary treatment[211,214,215]. Up to 30% of patients presenting with a LR may have underlying synchronous distant disease[216]. LR is associated with an increased risk for distant recurrence[217-219] and breast cancer death[220], which underlines the value of distant metastasis screening in these patients.

The time to LR has been proposed to be a prognostic factor of survival[218,221]: If LR occurs more than 2-5 years postoperatively, survival figures are better compared with earlier LR[222]. It is therefore hypothesized that LR developing within five years after cancer surgery may represent metachronous second primaries in the breast rather than a recurrence of the index lesion[223].

The incidence of LRR depends on the therapy given along with other established risk factors such as young age, late-stage diagnosis, dense breast tissue[224], lymphovascular invasion, multifocality, lymph node involvement, histologic grade, and extensive associated ductal carcinoma in situ (DCIS)[50,51,79,217,225-230].

1.4.2 Distant metastasis

A distant metastasis is defined as any other recurrence than LR and RR, most commonly localised to the skeletal system, the liver, the lung or the brain. The concept of tumour dormancy is supported by the fact that CTCs are detected in the blood of recurrence-free breast cancer patients up to 25 years after primary diagnosis[231,232]. CTCs may remain dormant until they are either reactivated or eliminated[206]. A reactivation may be initiated through new mutations, scattering of secondary micrometastases, and increased levels of cytokines and growth factors by trauma, illness or a new surgical procedure[233,234]. Lack of vasculature surveillance or inefficient immunosurveillance could further explain reactivation[193,235-240]. CTCs are suspected to originate from occult micrometastases[231], and recent advancements allow the detection and quantification of CTCs in peripheral blood[241,242]. A meta-analysis by Wen-Ting et al included 6712 breast cancer patients from 50 studies and found specific treatment modalities such as neoadjuvant chemotherapy to associate with reduced of CTC-positive rates, suggesting that CTCs can monitor treatment responses in breast cancer patients[243]. In patients with detectable CTCs, larger tumours, higher histologic tumour grade, and increased lymph node involvement are significantly more common than in CTC-negative patients[241,244].

1.4.3 Recurrence patterns

The time to as well as the pattern of recurrence differs according to breast cancer subtype; slow-growing ER-positive tumours are characterized with a prolonged period of DFS. The recurrence pattern for luminal A shows a slow risk increase reaching its peak after three years; in luminal B, however, most recurrences occur during the first five years[245,246]. The risk of recurrence in luminal tumours is relatively low but remains stable even after 10 years of follow-up. These subtypes have the lowest rate of distant metastases, which are predominantly bone metastasis[210]. Local and regional recurrence risk is lowest among luminal A tumours[246].

HER2-enriched tumours show a biphasic peak of recurrence: the first about twenty months after primary surgical treatment, with a greater risk if Ki67 is 14% or more, and the second peak after around 72 months, with a greater risk if Ki67 is lower than 14%[245]. HER2-enriched and TNBC tumours have the highest risk of recurrence during the first five years[210]. The HER2-enriched subtype is associated with increased rates of locoregional recurrences and distant metastasis in bone, liver and brain[210,246].

Triple-negative tumours commonly have a high proliferation rate and their recurrence risk peaks at nearly 18 months. Less common variants of TNBC with a low proliferation rate display a continuous risk curve[245]. TNBC is associated with a predilection of distant metastasis for lung, bone and brain[210].

1.5 SOCIOECONOMIC STATUS AND COMORBIDITY

1.5.1 Socioeconomic status

Socioeconomic status (SES) is a complex concept used broadly in the literature to cover factors including ethnicity, income, education, occupation type and housing[247,248]. SES is associated with the stage of breast cancer at diagnosis, and screening attendance for women with lower socioecomonic status is lower[249]. Individuals with a lower SES tend to receive chemotherapy less often, less expensive alternatives of endocrine treatment, and less extensive surgery[250-252]. Low socioeconomic status is further associated with worse breast cancer survival[253,254]. A Swedish study including 4 645 breast cancer patients showed, after adjustment for tumour size and age at diagnosis, that the risk of breast cancer death was 19% lower among women belonging to a household with a high compared to a low socioeconomic status (HR high versus low 0.81; 95% CI: 0.67-0.97)[255].

Also breast reconstruction is affected by socioeconomic factors, since women opting for breast reconstruction are more likely to be of higher socioeconomic status[256-259]. Received information on IBR prior to surgery is affected by patient ethnicity and education[260]. A systematic review showed that patients with lower median income and of lower socioeconomic groups are less prone to undergo any type of breast reconstruction[256]. Women with the highest probability of having an IBR are of caucasian origin, have a private health insurance, and live in areas with the highest rates of high-school education[247,261,262]. This was also valid in countries with general health care coverage of the reconstructive procedure, such as Canada and Denmark [256,263]. In Sweden, having a current employment and a high income per household is significantly associated with an IBR, as is patient-reported perceived preoperative information and the feeling of being involved in the decision-making process[264].

1.5.2 Comorbidity

Several definitions have been suggested for the term comorbidity, based on variations of a single core concept: the presence of more than one distinct health condition in an individual. Always used on a person level, distinctions are sometimes made based on the nature of the health condition, the relative importance of co-occurring conditions, and the chronology of their presentation[265,266].

Chronic diseases are more common among elderly patients, and cancer itself is a chronic disease with long-term consequences for health and quality of life, more prevalent among older

patients[265]. Underlying comorbidity among cancer patients is common, and data from the U.S. indicate that 40% of all cancer patients have at least one other chronic condition with the most common diagnoses being cardiovascular disease, metabolic illness, mental health disorders, and musculoskeletal conditions[267]. Fifteen percent have two or more chronic conditions[267].

Comorbidity affects cancer treatment since underlying comorbidity potentially affects cancer development, stage at diagnosis, treatment, and outcome of breast cancer patients[268]. Patients with comorbidities are less likely to receive immediate or delayed breast reconstruction[257,262,263,269], to tolerate systemic treatment[267,270] or radiotherapy[271], and have lower BCSS as well as overall survival rates[270,272].

1.5.2.1 Charlson comorbidity index

Charlson et al defined numerous clinical health conditions through reviewing hospital charts and assessing their relevance in the prediction of 1-year mortality. The Charlson Comorbidity Index (CCI) has since then been a useful tool for health researchers to measure the presence and severity of comorbid disease status[273,274]. The index provides an overall score for comorbidity based on complex values weighted by level of severity in 19 selected health conditions (myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular accidents, dementia, chronic obstructive pulmonary disease, connective tissue disease, peptic ulcer disease, mild/severe liver disease, uncomplicated /end-organ damage diabetes mellitus, hemiplegia, moderate to severe chronic kidney disease, solid tumour, leukaemia, lymphoma and HIV), scoring on a scale of 0-6 per condition, and further accounts for age.

1.5.3 Smoking

Smoking is a well-known risk factor associated with comorbidity, level of education, SES, and cancer, making it a confounding factor important to take into consideration. It does not only associate with the presence of comorbidity, but also with the comorbid disease outcomes[275,276]. People living below the poverty level and people having lower levels of educational attainment have higher rates of cigarette smoking than the general population[277-280]. Smoking is associated with increased breast cancer risk[281], and women with low and moderate levels of education show increased smoking habits along with an increased incidence of breast cancer, thereby suggesting an association between the two factors (HR=1.40, 95% CI 1.25-1.57 and HR=1.14,

95% CI 1.05-1.24, respectively)[282]. Current smokers have worse breast cancer survival (HR1.33; 95 % CI 1.28-1.38) when compared with former smokers and never-smokers (1.09; 1.06-1.13)[283,284].

From a surgical point of view, smoking is associated with impaired wound healing and higher risk of infection[285,286]; longer periods of smoking cessation decrease the incidence of postoperative complications[287]. Since smokers experience postoperative complications such as flap loss, hematoma or fat necrosis more often than non-smokers[288], DIEP flap reconstruction is performed on non-smokers only in Sweden.

1.5.4 Body mass index

With worldwide increasing rates of obesity, new challenges for surgeons are arising as high BMI is a proven risk factor in any surgery, including breast reconstruction[289]. Patients with a BMI >30 are more likely to experience surgical complications including wound dehiscence, hematoma, seroma formation, fat necrosis, partial or total flap failure, and hernia occurrence, as well as medical complications including deep venous thrombosis, pulmonary embolism, myocardial infarction, pneumonia, urinary tract infection, sepsis, and stroke[289]. Some suggest a linear relationship between increasing BMI and overall complication rates, although serious complications defined as partial or total flap failure and medical events including thromboembolic or cerebrovascular events remain relatively uncommon even in morbidly obese patients[290]. Swedish recommendations state that patients receiving autologous reconstruction should have a BMI ≤ 30[180,181].

1.6 HEALTH-RELATED QUALITY OF LIFE AND PATIENT-REPORTED OUTCOMES

The term health-related quality of life (HRQoL) is multidimensional and was first introduced by the World Health Organization (WHO) in the 1950s. Health was then defined as "a state of complete physical, mental and social well-being, and not merely the absence of disease or infirmity"[291]. HRQoL consists of the four aspects including physical, emotional, cognitive and social function, and further the symptoms and difficulties related to the disease[292]. HRQoL should be estimated by the individual herself and can vary over time[292].

One way to estimate HRQoL in breast cancer patients is through measuring patient-reported outcomes (PROs), including self-assessment surveys to measure patients' own perception of treatment outcomes. Such assessment may itself improve patient satisfaction with received care.

There is a variety of instruments to measure PROs in breast cancer patients[293,294], some of which are listed below:

- Satisfaction and Body Image Questionnaires, (BREAST-Q)
- European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer Module (EORTC QOL-C30 and QLQ-BR23)
- Functional Assessment of Cancer Therapy-Breast Cancer (FACT-B),
- Satisfaction with Life Domains Scale for Breast Cancer (SLDS-BC),
- Body Image after Breast Cancer Questionnaire (BIBCQ)
- Hopwood Body Image Scale (HIBS)
- Polivy Body Image Scale (PBIS)
- Michigan Breast Reconstruction Outcomes Study (MBROS)
- Breast Cancer Treatment Outcome Scale (BCTOS)
- Breast Cancer Chemotherapy Questionnaire (BCQ)
- Functional Assessment of Cancer Therapy-Endocrine System (FACTES)
- Mastectomy Attitude Scale (MAS)
- Breast Cancer Prevention Trial Symptom Checklist (BCPT)

The results regarding HRQoL following implant-based IBR or autologous reconstruction are diverse, but the majority of studies show higher scores in reconstructed patients compared with those undergoing mastectomy alone[96,117,120,156,295-317]. A study by Jeevan et al, however, found that the long-term quality of life in patients undergoing immediate or delayed implant-based breast reconstruction was not better than in those undergoing mastectomy alone [318]. Long-term investigations into HRQoL after IBR are scarce[318-320], including small and heterogeneous cohorts.

1.6.1 BREAST-Q

BREAST-Q is a condition-specific instrument measuring PROs in breast surgery patients, and was first available in English in 2009[321]. It was translated into Swedish in 2012. The survey quantifies the pre- and postoperative effect of cosmetic and reconstructive breast surgery on HRQoL on six scales: physical, psychosocial and sexual well-being, and satisfaction with breasts, outcome, and care. It provides meaningful and reliable information for use in both clinical practice and research[321,322] and has been validated for the assessment of HRQoL in European women[323-326].

BREAST-Q offers specific modules for mastectomy, breast-conserving therapy and breast reconstruction which are distributed pre- and/or postoperatively (see Figure 6). Each subscale produces an independent score from 0 to 100 where lower values indicate lower well-being or satisfaction. The latest version of BREAST-Q, version 2.0, was launched in May 2015 and includes an additional subscale for adverse effects of radiation along with a question on lymphedema under the subscale for physical well-being.

Figure 6. The BREAST-Q version 1.0 is divided into a quality of life and a satisfaction domain, each of which contains information in several subscales.

2 AIMS OF THE THESIS

The specific aims were:

I. To evaluate the oncological safety of nipple-sparing mastectomy by comparing its local recurrence rate with that after conventional mastectomy.

II. To evaluate the oncological safety of DIEP flap reconstruction by estimating the associated risk of breast cancer recurrence and comparing it with a matched control group of patients undergoing mastectomy without any delayed reconstruction.

III. To explore the associations between socioeconomic status, comorbidity and survival outcomes in patients undergoing DIEP flap reconstruction compared with a matched control group of patients undergoing mastectomy without any delayed reconstruction.

IV. To investigate the long-term effects of radiotherapy as measured by rates of implant failure and patient-reported outcomes, and investigate the frequency of reoperations and conversions to autologous breast reconstruction in the same cohort.

3 PATIENTS AND METHODS

3.1 COHORT STUDY DESIGN

Population-based studies investigate a defined population and aim to generate results that are generalisable to the entire population addressed in the study and not merely the included study population. One form of population-based investigation is the cohort study design, in which the study population (the cohort) is biased on a specific exposure and followed for a period of time. The outcome of interest is registered in exposed and unexposed individuals during the follow-up period and incidence rates in both groups then compared. Cohort studies represent a fundamental study design in epidemiology used in several scientific fields, and can be either of retrospective or prospective nature. In cohort studies, unlike clinical trials, there is no intervention, treatment or exposure administered to the study population, thereby classifying it as an observational study design. Common characteristics of the cohort are often controlled for in the statistical analysis, and both exposure and control variables are measured at baseline. Risk factors are studied without subjecting participants to those risk factors but rather by collecting data based on the individual lifestyle habit such as incidental exposure risk factors or self-administered exposure (such as smoking). Regression analysis can later be used to evaluate the extent to which the exposure or treatment variable contributes to the outcome of interest, while accounting for other contributing covariates.

3.1.1 Matched cohort design

In a matched cohort study, the exposed case is matched with one or several unexposed controls with regard to a chosen set of matching variables such as age, calendar year, gender, or residential area. As a result of the matching procedure, these matching variables have an equal distribution in both groups and thus no effect as confounders; in that manner, a study design may get as close to a randomized controlled trial as possible. Hazard ratios can subsequently be calculated for suspected risk factors, without the effect estimates being influenced by the confounding effect of the matched covariates. A difficulty in matching procedures is the effort and cost it may require to identify matched controls since cohort studies often contain large sample sizes.

3.2 SWEDISH REGISTERS AND DATA SOURCES FOR THIS THESIS

3.2.1 Swedish Personal Identity Number

All Swedish citizens are given a unique 12-digit personal identity number (PNR) at birth, thereby enabling crosslinking between a large number of Swedish national registers which are an invaluable resource to medical research. The PNR further enables tracking of individual medical records across health care services enabling population-based epidemiological research[327].

3.2.2 The National Quality Register for Breast Cancer

Whereas the Swedish Cancer Register includes data on date of diagnosis, invasiveness, clinical TNM stage and SNOMED coding for histological data on all tumour types, the National Quality Register for Breast Cancer (NKBC) provides detailed information specifically for breast cancer, including date and method of diagnosis, age, gender, invasiveness, tumour and lymph node characteristics, type of surgery, pathological data, and neoadjuvant or adjuvant treatment regimens. The register is updated according to information from the Total Population Register (TPR), the Swedish Cancer Register and the Swedish Cause of Death Register and provides nationwide coverage since 1992. In 2007, a harmonised online reporting platform was developed (Informationsnätverk för Cancervården, INCA) to enable an entirely digital data flow. The NKBC has a high validity of over 90%[328]. Registered treatments have been validated against medical charts, and a 94-96% of completeness and agreement was found[329].

For **study I-II,** variables extracted from the NKBC include date of diagnosis, date of mastectomy, tumour size in mm, clinical and pathological tumour stage, invasiveness, clinical and pathological axillary lymph node status, ER and PgR status (both available from 2001), Nottingham histological grade (NHG, available from 2004), HER2 status (available from 2005), and recommended oncological treatment.

3.2.3 Registers maintained by Statistics Sweden

Statistics Sweden, established in 1858, maintains national registers on Swedish statistics such as the Total Population Register (TPR) and the Longitudinal Integration Database for Health Insurance and Labour Market Studies (LISA). The LISA database further harbours the Swedish Register of Education, the Swedish Occupational Register and the Register on Income and Taxes (IoT).

3.2.3.1 The Total Population Register

The Total Population Register is a nationwide register maintained by Statistics Sweden, covering all individuals in Sweden since 1986. It includes anyone born in Sweden or intending to live in Sweden for more than one year[327]. This register is updated continuously, providing information on Personal Identity Number, gender, birthdate, marriage and partnership, residency, country of birth, migration in and out of Sweden, and date of death.

3.2.3.2 Longitudinal Integration Database for Health Insurance and Labour Market Studies

The LISA database integrates data from the labour market and educational and social sectors that were held as separate registers such as the Income and Taxes (IoT), the Swedish Register of Education and the Swedish Occupational Register until 1990, and is updated each year. This national register includes all individuals above 16 years of age. More specifically, it provides information on education, employment, income, country of birth, and parental countries of birth.

3.2.4 Registers maintained by the National Board of Health and Welfare

The governmental agency National Board of Health and Welfare is responsible for Swedish statistics concerning health and disease, including health care and causes of death.

3.2.4.1 The Swedish National Patient Register

The Swedish National Patient Register (NPR) is maintained by the National Board of Health and Welfare and was founded in 1964. Since 1987, complete coverage has been assured with more than 99% of all somatic and psychiatric discharge codes. The NPR further includes patient and geographic data, as well as administrative data about the in-hospital stay, and medical data. Diagnoses at hospital discharge are forwarded electronically to the NPR in a standardized procedure. Each discharge generates World Health Organization International Classification of Diseases-10th Revision (ICD-10) codes with main and contributory diagnoses specified. The validity of the register has been shown to be high[330].

For study III, data on diagnoses for calculation of the Charlson Comorbidity Index were extracted from the year prior to reconstruction or corresponding reference date and onwards. Up to 30 ICD-10 codes were obtained per case along with ICD-10 procedure codes.

Data on tumour characteristics, treatment, recurrence and death were verified by individual review of medical charts for all studies included in this thesis.

3.3 STUDY POPULATION

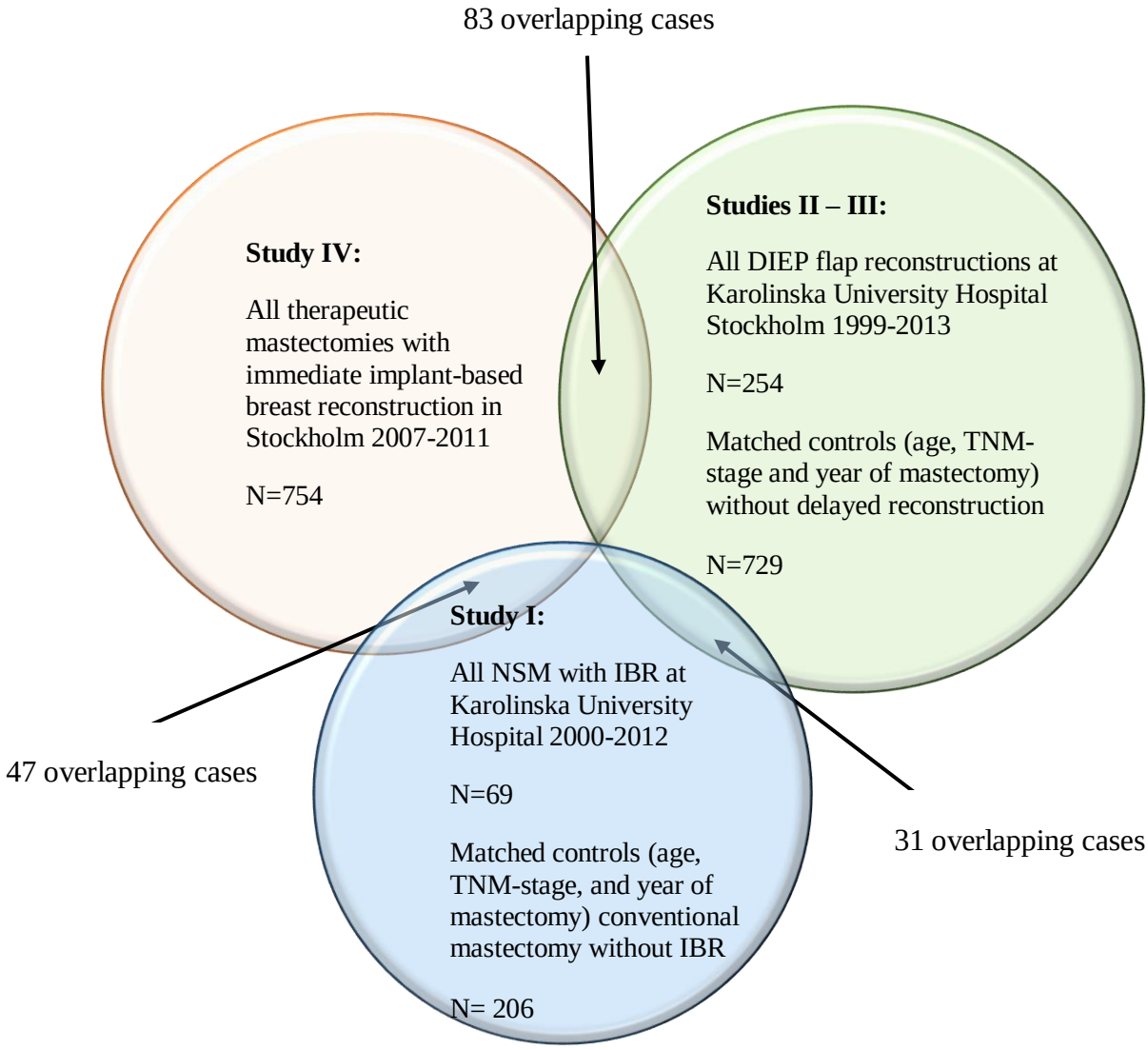


Figure 7. Schematic diagram showing all study cohorts included in this thesis.

3.4 STUDY I

Study I was a retrospective matched cohort study and included all breast cancer patients operated by therapeutic NSM and IBR at Karolinska University Hospital in Stockholm in 2000-2012. For each NSM patient, three matched controls were assigned with matching on TNM stage, year of mastectomy and age at mastectomy. Controls were breast cancer patients undergoing conventional mastectomy alone and were identified through the NKBC at the Regional Cancer Centre (RCC) in Stockholm.

Patients were divided into three age groups and two periods regarding the year of surgery. In case of neoadjuvant chemotherapy, matching used the preoperative clinical TNM stage. All preoperative mammography images of the NSM group were reviewed by a breast radiologist in order to define the radiological shortest distance (in mm) between the tumour border and the base of the nipple, defined as the tumour-nipple distance (TND).

Local recurrence (LR) was set as the primary endpoint. All histologically proven recurrent breast cancer in the ipsilateral skin, chest wall, or the nipple-areola-complex was categorized as LR. Apart from local recurrence-free survival (LRFS), BCSS, OS and disease-free survival (DFS) were assessed. Patients whose NAC had been removed postoperatively, i.e. due to a surgical complication or a positive retroareolar biopsy, were excluded from analyses.

Covariates collected for study I:

Birthdate, date of mastectomy, clinical and pathological tumour stage, invasiveness, invasive tumour size, mastectomy side, year of mastectomy, NHG, ER and PgR status, HER2 status, tumour multifocality, type of axillary surgery, number of lymph node examined, number of positive lymph nodes, TND, adjuvant radiotherapy, neo-/adjuvant chemotherapy, neo-/adjuvant endocrine therapy, neo-/adjuvant targeted therapy, LR, RR, distant metastasis, contralateral breast cancer, overall and breast cancer death, date of death, last date of follow-up, and date of medical chart review.

3.5 STUDIES II AND III

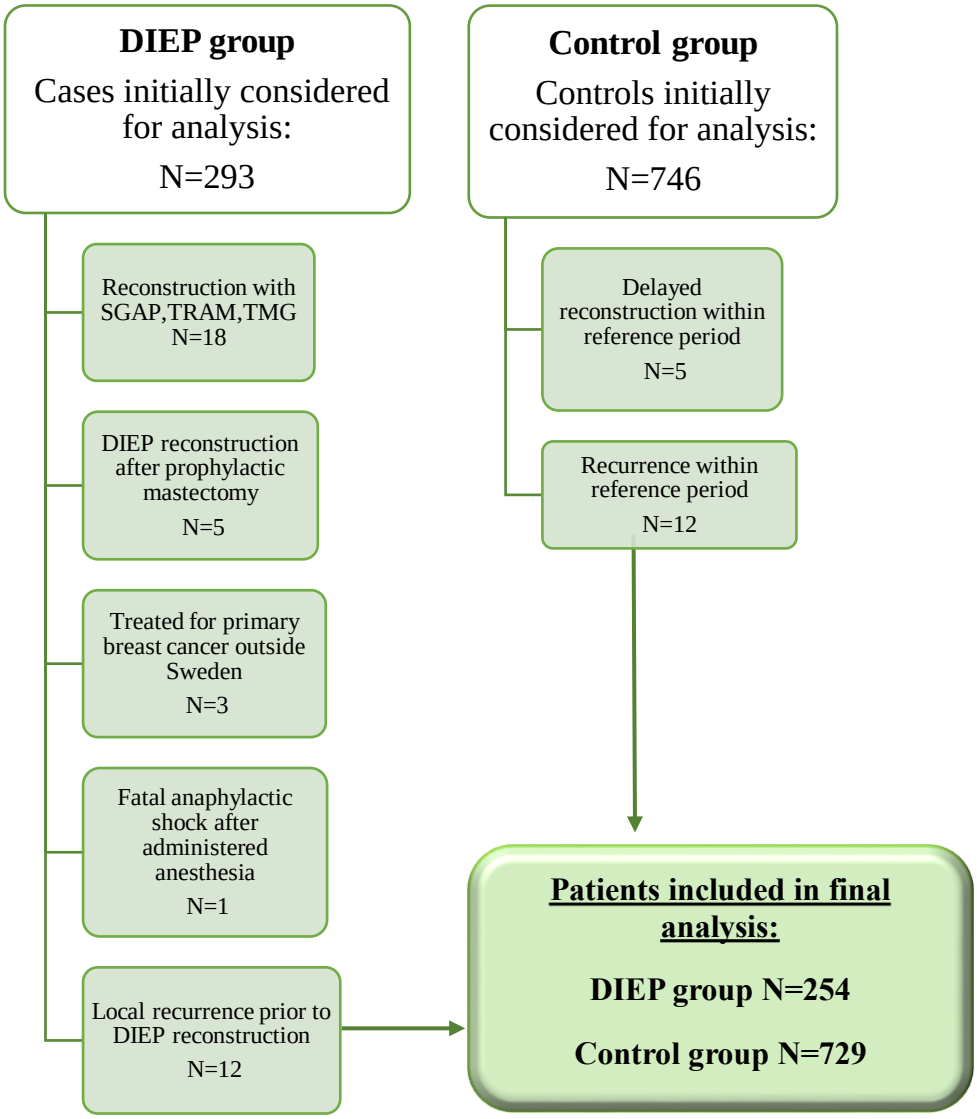


Figure 8. Flowchart for the inclusion in studies II and III. DIEP, deep inferior epigastric perforator flap; SGAP, superior gluteal artery perforator; TRAM, transverse rectus abdominis myocutaneous; TMG, transverse musculocutaneous gracilis.

Studies II and III are both based on the same retrospective matched cohort design including all patients with a previous mastectomy for breast cancer subsequently operated with a delayed DIEP flap breast reconstruction at the Department of Reconstructive Plastic Surgery at Karolinska University Hospital, Stockholm, between January 1999 and December 2013 (DIEP group). Patients in the DIEP group were matched to non-DIEP patients, i.e. breast cancer patients with a mastectomy but no delayed breast reconstruction, on the matching criteria year of and age at mastectomy, tumour stage, neoadjuvant therapy, and lymph node status.

Each DIEP patient was assigned a reference interval corresponding to the time between the date of mastectomy and the date of DIEP flap reconstruction. An index date based on individual

reference intervals for each DIEP case was applied to find three matched controls per DIEP case.

The primary endpoint was breast cancer-specific survival (BCSS). Secondary endpoints were OS and DFS. All included patients were free of recurrence and free of any other disseminated malignancy between the date of mastectomy and the date of DIEP reconstruction or the corresponding reference date.

Covariates collected for study II:

Birthdate, date of mastectomy, date of DIEP flap reconstruction, tumour stage, invasive tumour size, histological tumour type, BMI, smoking, mastectomy side, NHG, ER and PgR status, HER2 status, multifocality, type of axillary surgery, number of lymph nodes examined, number of positive lymph nodes, adjuvant radiotherapy, neo-/adjuvant chemotherapy, neo-/adjuvant endocrine therapy, neo-/adjuvant targeted therapy, surgical and medical complications, reoperations and revision surgery, LR, RR, distant metastasis, contralateral breast cancer, overall and breast cancer death, date of death, last date of follow-up, and date of medical chart review.

In study II, patients undergoing an immediate implant-based breast reconstruction (IBR) had not been excluded since IBR does not affect the primary outcome, survival. Those IBR cases were thus also included in study III since it is based on the same cohort. Sensitivity analyses were carried out in order to analyse the impact of IBR on both OS and BCSS.

In study III, individual data on socioeconomic factors were obtained from Statistics Sweden and data on comorbidity from the National Board of Health and Welfare. Three-digit ICD-10 codes were assigned to the groups of diagnoses used in the Charlson Comorbidity Index (CCI) [273,274]. The breast cancer diagnosis itself was not included in the CCI score.

Additional covariates collected for study III

Disposable household and individual income, family status (i.e. living in a partnership or in a single household), highest level of education attained, occupation, country of birth, country of birth for parents, and up to 30 ICD-10 codes per case.

3.5.1 Timescales for investigated endpoints studies I-III

In study I, LRFS was calculated from the date of mastectomy until the date of a local recurrence diagnosis, or to any first event of any local, regional or distant recurrence (disease-free survival, DFS). BCSS was calculated from the date of surgery to the date of death due to breast cancer, and OS was calculated from the date of surgery to the date of death from any cause.

In study II-III, survival was calculated from the date of DIEP reconstruction, or the index date, until the date of any first local, regional or distant recurrence [DFS], the date of death due to breast cancer [BCSS], or the date of death by any cause [OS], respectively.

In the absence of any event, cases were censored at the date of last clinical follow-up for LRFS and DFS, and last medical chart review for BCSS and OS.

3.6 STUDY IV

Study IV is a follow-up on a previously published retrospective cohort study by our group [175]. The cohort consists of all breast cancer patients operated with a therapeutic mastectomy and implant-based IBR between January 2007 and December 2011 at Stockholm's four main hospitals (Karolinska University Hospital, Capio St. Göran's Hospital, Southern General Hospital, and Danderyd Hospital). Three groups were identified: those not receiving any radiotherapy (RT), those who had received RT prior to IBR (i.e. after previous breast-conserving surgery or due to other malignancies), and those with post-mastectomy RT.

The primary endpoint was IBR failure, defined as the removal of the implant due to surgical complications or patient preference, with or without a simultaneous or subsequent autologous reconstruction. Secondary endpoints were PROs, the number of unplanned reoperations and the conversion rate to autologous reconstruction.

3.6.1.1 Patient-reported outcomes

The BREAST-Q postoperative reconstruction module with subscales for satisfaction with breasts and with overall outcome, psychosocial, sexual and physical well-being was used. In order to enable comparison with the scores from 2012, the BREAST-Q version 1.0 was applied again. Questionnaires were sent out approximately eight years after the previous investigation. Postal addresses were obtained from the Swedish Tax Agency.

Covariates collected for study IV:

Birthdate, date of mastectomy/IBR, tumour stage, invasive tumour size, mastectomy side, year of mastectomy, NHG, type of axillary surgery, number of lymph nodes examined, number of positive lymph nodes, radiotherapy, neo-/adjuvant chemotherapy, neo-/adjuvant endocrine therapy, neo/adjuvant targeted therapy, contralateral breast cancer, conversion to autologous reconstruction, recurrence, overall and breast cancer death, date of death, date of last follow-up and date of medical chart review. Radiotherapy details included irradiation field, fractions, cumulative dose, and date of last given fraction.

Postoperative surgical complications: postoperative infection and reoperations for deep infection or bleeding, implant removal, and non-surgically treated complications such as infection, hematoma, and seroma.

Revisional surgery regarded the ipsilateral breast, i.e. capsulectomy, implant exchange, abdominal advancement flap, nipple reconstruction, liposuction, lipofilling, and scar revision. Contralateral symmetrizing procedures included mastopexy, breast reduction, and implant-based augmentation.

3.7 STATISTICAL ANALYSES

The normal distribution of data was tested through the Shapiro–Wilks test, and parametric or non-parametric tests were used accordingly. For continuous variables, mean or median values were reported with their standard deviation and range, respectively. In case on non-normal distribution, Mann-Whitney or Kruskal Wallis tests were applied for two-group or three-group comparisons, respectively. Categorical data are presented as case numbers, and their distribution in the groups was tested by Pearson's Chi square test or Fisher's exact test.

The reported P-values are two-tailed, with a P-value of <0.05 considered significant. SPSS® version 24-26 (IBM, Armonk, New York, USA) and Stata version 16 (StataCorp, Lakeway Drive, Texas, USA) were used for all statistical analyses, and resulting databases were registered and managed in accordance with the European General Data Protection Regulation.

3.7.1 Survival analyses

Survival analyses can be applied on any event of interest, not merely death, comparing binary outcomes between two groups of exposed versus unexposed individuals. Since survival analyses are so called time-to-event analyses, a timescale must be predefined. Depending on the outcome of interest, the timescale could include different definitions such as follow-up time, attained age, etc. For follow-up, time zero represents the start of the observation time. In all our studies, time zero was set at time of reconstruction, either immediate or delayed.

Each case further contributes to person-time until the occurred event of interest or until the time the case is removed, i.e. censored, due to drop-out or loss to follow-up, or until the end of follow-up time. Merely comparing the number of outcomes at the end of the follow-up period would not account for variations in person-time contributed by each case and would hence give misleading results. The censoring in survival analysis should not be related to the probability of the event of interest, i.e. it should be unrelated to the outcome, so called non-informative censoring.

One type of survival analysis is the use of Kaplan-Meier survival estimates, used in all studies of this thesis. The Kaplan-Meier model estimates the survival function over time and thereby the risk of an event by quantifying the time until the occurrence of the event. The estimated survival curves can be plotted overall or by groups of interest and in order to do so, the status at the last observation and the start and end date of follow-up time must be included for all cases. The plot will display a step-wise declining function as events occur, and censored cases

are denoted by small vertical marks. In this thesis, survival proportions were calculated according to the Kaplan Meier model, and the log rank test or Wilcoxon test were applied accordingly to compare groups. Due to the declining number of cases over time, the estimated probability of survival is more precise at the start than towards the end of follow-up. Another limitation of the Kaplan-Meier survival model is that it does not account for the associations of the outcome with several covariates (multivariable analysis), and further methods such as the Cox proportional hazard regression model must then be applied.

3.7.1.1 Cox proportional hazards regression model

Another method of survival analysis is the Cox proportional hazards regression model. Also in Cox proportional hazards regression, the timescale must be predefined. The advantage of this method is that the association of several covariates with the outcome can be assessed and adjusted for. No assumption about the shape of the hazard is made, and the baseline hazard in a Cox regression model is hence unknown but considered equal for all cases. The regression model assumes, however, that hazard is proportional for each time point. Since this assumption cannot always be fulfilled, it should be assessed before the performance of analyses. One way of doing this is by visually assessing the plot of Schoenfeld's residuals against time. Another assumption made by the Cox proportional hazards model is that censoring is non-informative. In study II-IV, Cox proportional hazard regression was applied to assess the association of risk factors with the relevant endpoints.

In study II-III, uni- and multivariable Cox proportional hazards regression analyses were carried out to assess associations of comorbidity (categorized through the CCI score), socioeconomic factors (including disposable income per household, family status, highest level of education and occupation), and clinical data (year of and age at mastectomy, tumour stage, lymph node status, hormone receptor status, radio- and chemotherapy) with OS and BCSS.

In study IV, uni- and multivariable Cox proportional hazards regression were applied to test risk factors for IBR failure. The proportional hazards assumption was checked through statistical testing and graphical diagnostics based on the global test of Schoenfeld's residuals without any evidence of time-varying hazards. Results are presented as hazard ratios (HR) with their 95% confidence intervals (CI).

4 RESULTS

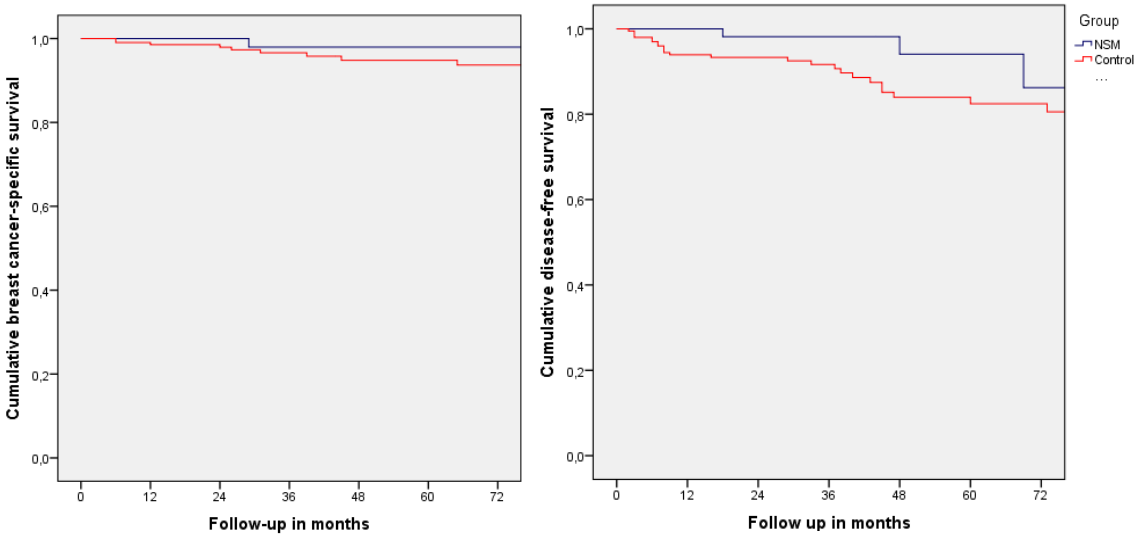
4.1 STUDY I

A total of 275 mastectomies were included in the study; 69 (in 67 patients) in the NSM group and 206 (in 203 patients) in the control group. The median age was similar between both groups: 49 years (24-74) for the NSM group and 48.5 years (21-87) for the control group (P= 0.384). There were no statistically significant differences between the two groups regarding neoadjuvant or adjuvant oncological treatment. Median follow-up time was 36 months (range 4-162) for the NSM group and 35 months for the control group (range 1-160; P= 0.969). The TND measurements could be re-assessed in 56 out of 69 in the NSM group, and the median TND was 49.5 mm (1-120 mm). NSM patients operated 2010-2012 showed a trend towards shorter median TND than those operated 2000-2009 (4.9 versus 5.3 cm, P=0.590). The NAC was successfully preserved in 64 out of 69 cases.

4.1.1 Breast cancer recurrence and survival

Breast cancer recurrence occurred 29 cases during follow-up: three in the NSM group (one regional relapse which coincided with distant metastases, one isolated regional relapse and another case of distant metastasis) and 26 in the control group. No LR (including NAC recurrences) were registered in the NSM group throughout the entire follow-up period whereas seven LR were reported in the control group (P=0.140). Median time to LR was 11 months (range 3-92). An additional five regional and 19 distant recurrences were registered in the control group. The 5-year DFS was 94.1% in the NSM group and 82.5% in the control group (log rank P=0.068; see Figure 9).

Death of any cause occurred in twenty-three cases, thirteen of which were due to breast cancer. Two cases of death due to any cause were registered in the NSM group, including one breast cancer death. Twenty-one deaths of any cause were registered in the control group, twelve of which were breast cancer deaths. The estimated 5-year OS was 96.2% in the NSM group and 91.3% in the control group (log rank P=0.166). Five-year BCSS was 98.0% in the NSM group and 94.8% in the control group (log rank P=0.244; see Figure 9).



Women at risk

NSM	69	62	53	41	33	23	14	69	59	47	34	22	15	8
Control group	206	193	162	124	93	86	75	204	162	126	95	69	54	43

Figure 9. Kaplan-Meier survival curves for BCSS (left) and DFS (right) with the blue curve representing the NSM group and red curve the control group in both plots. Log rank P=0.244 (BCSS) and P=0.068 (DFS).

4.2 STUDY II

The cohort in studies II-III consisted of 983 patients: 254 DIEP flap reconstructions matched to 729 controls. The median time from mastectomy to DIEP flap reconstruction was 36 (range 12–220) months, with a median follow-up of 89 (range 4–214) months following DIEP flap reconstruction and 75 (0–367) months (P=0.053) in the control group. The median invasive tumour size was similar in both groups: 28.5 mm (1–100) and 30 mm (1–170), respectively (P=0.540). The median time between DIEP flap reconstruction/index date and breast cancer recurrence was 74.5 and 60.5 months, respectively (P=0.339).

4.2.1 Breast cancer recurrence and survival

A total of 224 recurrences were registered, with similar proportions for both groups: 50 (19.7%) recurrences in the DIEP group and 174 (23.9%) in the control group (P=0.171). Eleven (4.3%) LR occurred in the DIEP group and 31 (4.3%) in the control group (P=0.958). RR were

registered in eight (3.1%) and 33 (4.5%) cases, respectively (P=0.344), while distant recurrence developed in 43 (16.9%) and 149 (20.4%) cases, respectively (P=0.224).

Thirty-seven (14.6%) deaths due to any cause were registered in the DIEP group and 188 (25.8%) in the control group (P<0.001), with a 5-year overall survival of 91.6% and 84.7%, respectively (log rank P<0.001; see Figure 10). Breast cancer death was reported in 33 (13.0%) women in the DIEP group and 132 (18.1%) in the control group (P=0.060). Unadjusted Kaplan Meier estimates showed a 5-year BCSS of 92.0% and 87.9% (log rank P=0.032; see Figure 10). Independent risk factors for death due to breast cancer are reported in Table 3. After adjustment for tumour and patient characteristics and treatment, the lower OS persisted for the control group. This was, however, not seen for BCSS. With these results in mind, we planned study III in order to investigate potential underlying differences between the two cohorts, such as SES or comorbidity.

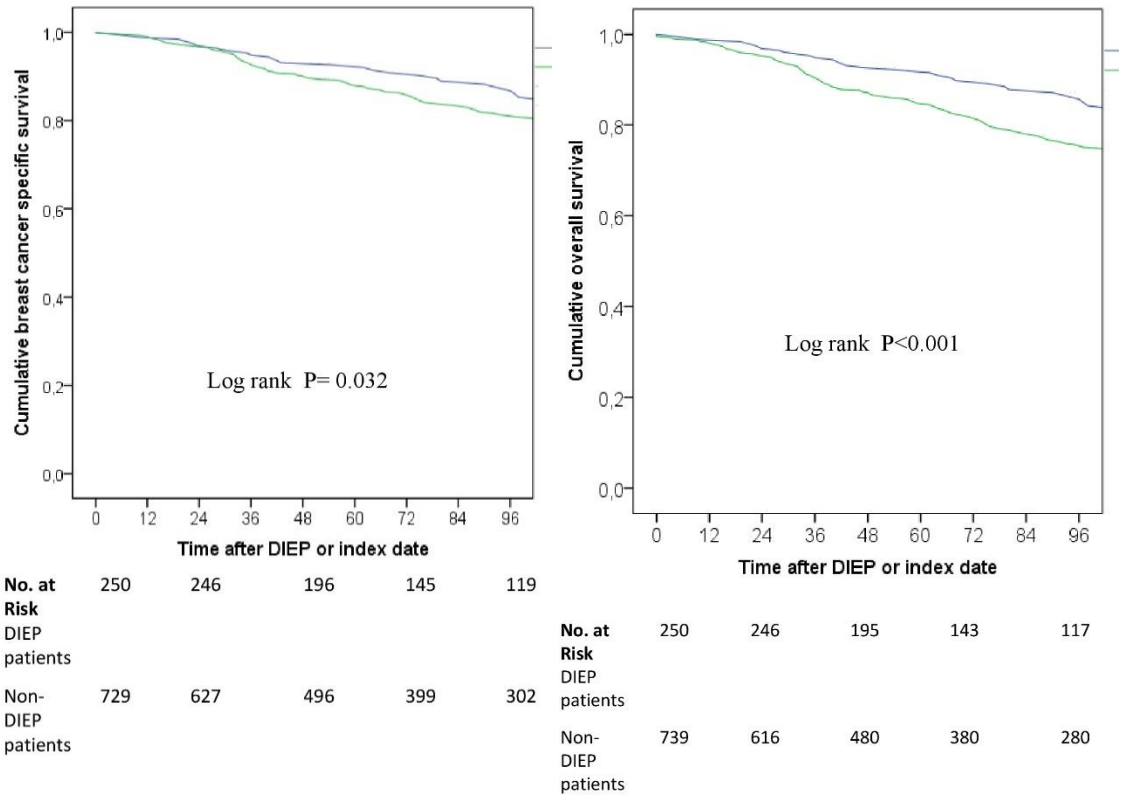


Figure 10. Unadjusted Kaplan-Meier survival curves for BCSS (left) and OS (right) with the blue curve representing the DIEP group and the green curve the control group in both plots. Log rank P=0.032 (BCSS) and P<0.001 (OS).

Table 3. Uni- and multivariable Cox proportional hazards regression analysis with BCSS as endpoint

	Univariable analysis		Multivariable analysis	
	Hazard ratio	*P*	Hazard ratio	*P*
Cohort				
DIEP	1.00 (reference)		1.00 (reference)	
Control	1.52 (1.03, 2.22)	0.033	1.35 (0.80, 2.26)	0.263
Age at mastectomy				
≤ 40	1.00 (reference)		1.00 (reference)	
41–50	0.87 (0.58 ,	0.484	0.66 (0.38, 1.16)	0.149
≥ 50	1.29)	0.127	0.85 (0.50, 1.45)	0.550
	0.73 (0.48, 1.09)			
Year of mastectomy				
1980–1999	1.00 (reference)		1.00 (reference)	
2000–2005	0.78 (0.55, 1.10)	0.164	0.53 (0.30, 0.94)	**0.029**
2006–2012	0.59 (0.37, 0.96)	0.034	0.34 (0.18, 0.66)	**0.001**
Invasive tumour category				
T1	1.00 (reference)		1.00 (reference)	
T2	1.09 (0.74, 1.60)	0.665	1.52 (0.80, 2.91)	0.206
T3	1.98 (1.29, 3.03)	0.002	2.22 (1.07, 4.62)	**0.032**
Nottingham Histological Grade				
I	1.00 (reference)		1.00 (reference)	
II	1.69 (0.61, 4.72)	0.314	1.45 (0.44, 4.84)	0.543
III	1.98 (0.71, 5.51)	0.191	1.79 (0.53, 6.10)	0.353
Oestrogen receptor status				
Negative	1.00 (reference)		1.00 (reference)	
Positive	1.26 (0.87, 1.81)	0.229	3.58 (1.42, 9.00)	**0.007**
Progesterone receptor status				
Negative	1.00 (reference)		1.00 (reference)	
Positive	0.98 (0.70, 1.37)	0.905	1.12 (0.63, 2.02)	0.698
Lymph node status				
Node-negative	1.00 (reference)		1.00 (reference)	
Node-positive	2.48 (1.75, 3.52)	<0.001	2.19 (1.21, 3.97)	**0.010**
Radiotherapy				
Yes	1.00 (reference)		1.00 (reference)	
No	0.53 (0.38, 0.76)	0.001	0.74 (0.41, 1.35)	0.330
Chemotherapy				
Yes	1.00 (reference)		1.00 (reference)	
No	0.59 (0.41, 0.87)	0.007	0.694 (0.33, 1.48)	0.345
Endocrine therapy				
Yes	1.00 (reference)		1.00 (reference)	
No	1.06 (0.76, 1.47)	0.750	2.83 (1.18, 6.76)	**0.019**

4.3 STUDY III

The cohort in study III is identical to the one in study II. The results presented in Table 4 suggest that the DIEP group represents a population with a higher SES, since a lower proportion of individuals with primary school as the highest level of education or a low income were seen (Table 4). The DIEP group had a significantly lower prevalence of congestive heart failure, diabetes mellitus and chronic obstructive pulmonary disease, and lower overall CCI scores compared with the matched control group.

Interestingly, we found that significantly more cases in the control group than the DIEP group had previously undergone IBR (149 cases (20.4%) versus 21 cases (8.3%), P<0.001). We therefore compared women without IBR from the control group with women with IBR from both groups, and found that the IBR patients had characteristics similar to the DIEP group. Women with an IBR had more often higher education levels (postsecondary > 3 years, 40.6% versus 26.8%, P=0.001) and a high disposable household income (46.5% versus 28.1%, P<0.001), and worked more often as clerks/civil servants (62.3% versus 35.3%, P<0.001). A majority of women undergoing IBR were in the lowest CCI group (CCI group 0-6: 90.0% versus 67.2%, P<0.001). The differences between the DIEP and the control group persisted, however, when excluding all IBR cases from the analysis of socioeconomic characteristics and comorbidity. The control group had a higher crude risk of death of any cause (HR 2.08, 95% CI 1.40-3.09), which persisted despite adjustment for clinicopathological factors, SES and comorbidity (HR 1.88, 95% CI 1.24-2.86). Younger age at mastectomy, being retired or unemployed, and having a CCI score ≥ 7 were further presented as independent risk factors. On sensitivity analyses excluding all women with IBR, similar results were found.

For BCSS, the higher crude risk of breast cancer death (HR1.62, 95% CI 1.07-2.46) in the control group did not persist in adjusted analyses. When we excluded all IBR cases from multivariable analysis, however, BCSS was significantly lower for the control group (HR 1.79, 95% CI 1.09-2.92). Independent risk factors for death due to breast cancer were younger age at mastectomy, working as a labourer or being unemployed, and a CCI score ≥ 7.

Table 4. Socioeconomic data and comorbid conditions comparing the DIEP and control groups.

	DIEP group (n = 254)	***Control group (n = 729)***	***P-value***
Family status			**0.024***
Partner/married	145 (57.1)	406 (55.7)	
Single	107 (42.1)	311 (42.7)	
Missing	*2 (0.8)*	*12 (1.6)*	
Own birth country			0.243
Sweden	187 (73.6)	574 (78.7)	
Europe, not Sweden	38 (15.0)	89 (12.2)	
Outside of Europe	29 (11.4)	66 (9.1)	
Missing	*0 (0)*	*0 (0)*	
Highest level of education			**0.026**
Primary school	29 (11.4)	118 (16.2)	
Secondary school	110 (43.3)	273 (37.5)	
Postsecondary school, < 3 years	52 (20.5)	111 (15.2)	
Postsecondary school, ≥ 3 years	63 (24.8)	218 (29.9)	
Missing	*0 (0)*	*9 (1.2)*	
Occupation			0.086
Clerk/civil servant	136 (53.5)	334 (45.8)	
Entrepreneur	6 (2.4)	27 (3.7)	
Labourer	47 (18.5)	119 (16.3)	
Unemployed/retired	55 (21.7)	204 (28.0)	
Missing	*10 (3.9)*	*45 (6.2)*	
Income per person			**<0.001**
Low	61 (24.0)	266 (36.5)	
Middle	112 (44.1)	215 (29.5)	
High	81 (31.9)	245 (33.6)	
Missing	*0 (0)*	*3 (0.4)*	
Income per household			0.287
Low	75 (29.5)	252 (34.6)	
Middle	87 (34.3)	240 (32.9)	
High	92 (36.2)	234 (32.1)	
Missing	*0 (0)*	*3 (0.4)*	
Congestive heart failure			**0.030**
Yes	5 (2.0)	36 (4.9)	
No	248 (97.6)	649 (89.0)	
Missing	*1 (0.4)*	*44 (6.0)*	
Pulmonary disease			**0.003**
Yes	5 (2.0)	46 (6.3)	
No	248 (97.6)	639 (87.7)	
Missing	*1 (0.4)*	*44 (6.0)*	
Diabetes			**0.029**
Yes	6 (2.4)	40 (5.5)	
No	247 (97.2)	645 (88.5)	
Missing	*1 (0.4)*	*44 (6.0)*	
Median CCI Score	1 (range 0-13)	2 (range 0-16)	**0.021**

4.4 STUDY IV

A total of 754 implant-based immediate breast reconstructions (IBR) in 729 women were included. The cohort was divided into radiotherapy (RT) groups: 386 non-irradiated IBRs, 64 IBRs after previous RT, and 304 IBRs receiving PMRT. Median follow-up time was 120 months (range 1-171 months) and did not differ between RT groups (P=0.111).

IBR failure, defined as implant removal due to any cause with or without an autologous reconstruction, occurred after 128 IBRs (17%). Significantly higher proportions of IBR failure were registered in irradiated breasts, specifically in those which had been subjected to RT prior to IBR. Risk factors for IBR failure are presented in Table 5. We found prior or postoperative RT, age > 50 years at the time of IBR, BMI ≥ 25, and surgical complication after IBR to be independent risk factors for IBR failure while being operated with permanent implants was negatively associated with IBR failure.

At least three unplanned reoperations were performed in 98 out of 751 IBRs: 7.8% in the non-irradiated group, 7.8% in the prior RT and 20.8% in the postoperative RT group (P<0.001). Minor or major surgical postoperative complications were registered after 223 (29.6%) and 40 (5.3%) IBRs, respectively, and the rate of complications did not differ between the groups.

BREAST-Q questionnaires were sent out to all patients alive who had not reached the primary endpoint IBR failure according to medical charts. In total, 540 patients were eligible, 390 of whom returned the survey. The response rate was thus 72.2%. A higher proportion of smokers (19.3 versus 12.3%, P=0.045) and of women suffering a breast cancer recurrence (12.7 versus 5.6%, P=0.006) was found among non-responders. Within-group longitudinal analysis of BREAST-Q scores showed a significant decrease in mean scores for satisfaction with breasts and with overall outcome in the non-irradiated group (P<0.001 and P=0.004), while an increase in mean score was found on the psychosocial well-being subscale for postoperatively irradiated cases (P=0.011, see Table 6). On adjusted linear regression analysis of differences between RT groups based on the 2020 survey, women who had received prior RT scored lower on all subscales except for psychosocial well-being. Women in the postoperative RT group, however, reported significantly lower scores on the physical well-being subscale only.

Table 5. Uni- and multivariable Cox regression analyses with IBR failure as outcome variable, defined as implant removal due to any cause, with or without a contemporary or subsequent autologous reconstruction. Analyses include only cases with non-missing information in all covariates in both models. RT Radiotherapy IBR immediate breast reconstruction

	Number of cases	***Number of events***	***Univariable analysis***		***Multivariable analysis***	
	715	**125**	**Hazard ratio (95% CI)**	**P-value**	**Hazard ratio (95% CI)**	**P-value**
Radiotherapy group						
No RT	362	34	*1.00 (reference)*		*1.00 (reference)*	
Prior RT	54	18	4.32 (2.44-7.65)	**<0.001**	4.65 (2.55-8.45)	**<0.001**
Postoperative RT	299	73	2.87 (1.91-4.31)	**<0.001**	3.42 (2.24-5.23)	**<0.001**
Smoking						
No	605	98	*1.00 (reference)*		*1.00 (reference)*	
Yes	110	27	1.59 (1.04-2.44)	**0.033**	1.33 (0.86-2.06)	0.199
BMI						
<25	460	63	*1.00 (reference)*		*1.00 (reference)*	
≥ 25	255	62	1.96 (1.38-2.78)	**<0.001**	1.49 (1.03-2.14)	**0.034**
Age at IBR						
≤40 years	147	17	*1.00 (reference)*		*1.00 (reference)*	
41-50 years	271	41	1.35 (0.77-2.38)	0.295	1.54 (0.86-2.75)	0.146
51-65 years	240	53	2.05(1.19-3.54)	**0.010**	2.59 (1.43-4.67)	**0.002**
≥66 years	57	14	2.41 (1.19-4.89)	**0.015**	2.63 (1.23-5.61)	**0.012**
Type of implant						
Temporary expander	236	44	*1.00 (reference)*		*1.00 (reference)*	
Permanent expander	311	61	1.06 (0.72-1.57)	0.754	0.92 (0.62-1.38)	0.691
Permanent implant	168	20	0.59 (0.35-0.99)	**0.047**	0.47 (0.27-0.83)	**0.009**
Surgical complications						
None	464	48	*1.00 (reference)*		*1.00 (reference)*	
Minor	212	58	2.94 (2.00-4.31)	**<0.001**	2.76 (1.87-4.08)	**<0.001**
Major	39	19	7.21 (4.24-12.28)	**<0.001**	8.84 (5.09-15.36)	**<0.001**

Table 6. Each BREAST-Q subscale in the three radiotherapy groups is presented for both surveys, i.e. 2012 and 2020. Change in mean from the first to the second survey is shown, as well as the results of a dependent sample t-test comparing scores at the two different time points.

BREAST-Q subscale	**Cases in the analysis**	**Mean score 2012**	**Mean score 2020**	**Change in mean**	**P- value**
Satisfaction with breasts					
Non-irradiated	217	59.30	55.30	-3.97	**<0.001**
Prior RT	21	46.50	43.50	-3.00	0.279
Postoperative RT	144	52.04	52.64	0.60	0.615
Satisfaction with overall outcome					
Non-irradiated	216	71.36	67.68	-3.68	**0.004**
Prior RT	21	58.59	52.77	-5.82	0.242
Postoperative RT	144	65.79	66.66	0.87	0.554
Psychosocial well-being					
Non-irradiated	203	73.12	72.38	-0.75	0.590
Prior RT	21	61.41	62.41	1.00	0.752
Postoperative RT	144	65.70	69.81	4.11	**0.011**
Sexual well-being					
Non-irradiated	177	56.50	54.53	-1.97	0.189
Prior RT	21	42.57	35.48	-7.10	0.053
Postoperative RT	138	49.06	49.21	0.15	0.938
Physical well-being					
Non-irradiated	203	80.23	81.09	0.87	0.360
Prior RT	21	73.36	75.09	1.73	0.457
Postoperative RT	144	76.00	76.24	0.24	0.828

5 DISCUSSION

In this thesis, two common breast reconstruction methods were investigated: immediate implant-based breast reconstruction and delayed DIEP flap reconstruction. Firstly, oncological safety in terms of recurrence risk and survival was assessed. Secondly, we added aspects of socioeconomic status (SES) and comorbidity to the oncological outcomes in patients undergoing delayed DIEP flap reconstruction. Finally, we investigated the effects of prior or postoperative radiotherapy (RT) on immediate implant-based breast reconstruction, reporting IBR failure rates, number of unplanned reoperations and patient-reported outcomes (PROs).
In **study I**, survival was better in NSM patients with IBR than in the matched control group. The same was found in **study II** which included patients undergoing delayed DIEP flap reconstruction, despite satisfactory matching procedures in both studies. **In study III**, a stronger socioeconomic status and a lesser degree of comorbidity were found in DIEP patients compared with the matched control group; the superior survival was retained despite adjustment for these factors. **Study IV** presents a long-term follow-up of a large cohort of breast cancer patients with implant-based IBR showing that both prior and postoperative RT significantly increase the risk of IBR failure and negatively affect patient-reported outcomes.

There are no national data on the number of delayed DIEP flap reconstructions performed in Sweden. In Stockholm, fewer delayed DIEP flap reconstruction than implant-based IBR are performed, and the DIEP procedure was initially reserved for irradiated patients and those experiencing IBR failure. This may, however, be different to other Swedish regions: In a recent Swedish study, wide regional variations in breast reconstruction patterns were reported, possibly due to limited availability of plastic and breast surgeons and the lack of standardized indications for breast reconstruction. Of 2904 mastectomy patients responding to the questionnaire, 31% reported having had a breast reconstruction (implant-based in 58% , autologous in 31% and methods of reconstruction unknown in 11%), which was most commonly (80%) performed in a delayed setting. Radiotherapy and older age was found to negatively associate with receiving breast reconstruction, even though autologous delayed reconstructions would be expected to be used especially in the context of radiotherapy [331].

5.1 RECURRENCE AND SURVIVAL

In both **study I and II**, higher proportions of recurrence were found in the control groups. While Benediktsson and colleagues found high proportions of LR and NAC involvement in the setting of NSM[145], the majority of studies confirm that NSM is an oncologically safe procedure with low local recurrence rates[93,134,142,147]. Coopey and colleagues attributed the low recurrence rates among NSM patients to improved patient selection over time since positive subareolar biopsies were shown to decrease[93]. Our results are hence in line with others, suggesting that NSM with subsequent implant-based IBR can be considered an oncologically safe procedure with no adverse effect on cancer-specific outcomes[154,155].

For delayed DIEP flap reconstruction, the oncological safety has been a subject of concern since surgical trauma and postoperative complications may exert systemic inflammatory effects which are hypothesized to negatively influence the oncological outcome[332-335]. Some previous studies have suggested higher recurrence rates after large flap reconstructions[197,198], while other studies, none of which specifically investigated DIEP flap reconstruction, did not confirm any increased recurrence risk[199,201]. In **study II**, we found no evidence of an increased recurrence risk after delayed DIEP flap reconstruction, which is supported by results from another matched cohort study from the Uppsala region in Sweden[202]. Here, a higher proportion of patients in the DIEP cohort than in the no-DIEP cohort received adjuvant treatment ($P<0.0001$), which is concordant with our findings, as was the overall local recurrence rate. Thus, we delivered further evidence that DIEP flap reconstruction is not associated with an increased risk of breast cancer recurrence.

In **study I**, disease-free, overall and breast cancer-specific survival were worse for women undergoing conventional mastectomy without implant-based IBR, even though the difference did not reach statistical significance. In **studies II-III**, however, this phenomenon was stronger, especially regarding overall survival. A systematic review and meta-analysis by De la Cruz et al included 20 studies investigating DFS and OS in NSM, a majority of which showed superior survival in the NSM groups when compared with patients undergoing conventional mastectomy or SSM[155]. Likewise, a number of studies suggest superior survival in delayed autologous flap reconstruction[200,202]. A majority of previous studies are in line with our results concluding that DIEP flap reconstruction is not associated with worse survival. Importantly, it would be inaccurate to conclude that an IBR or delayed autologous flap reconstruction such as DIEP would actually improve breast cancer survival. Instead, these findings should suggest

selection mechanisms and thus potential differences between the reconstructed and the control groups which were unaccounted for in analyses.

Smokers and patients with a high BMI (>30) are normally not admitted to receive implant-based IBR or delayed DIEP flap reconstruction since these are known risk factors for adverse surgical outcomes such as infection, wound dehiscence and reconstructive failure. Therefore, a higher prevalence of these factors, also increasing the risk of recurrence and survival, may have been present in the control groups. In **studies I-III**, data on these factors were incomplete and could unfortunately not be investigated. Stage at diagnosis, treatment, comorbidity and SES further affect who is offered breast reconstruction[261,263,336]. SES affects the access to breast reconstruction whilst comorbidities greatly influence the selection of patients for reconstruction[102,261,263,269,270,337,338]. More importantly still, all these factors are intricately associated with each other and with survival outcomes (see Figure 11).

Thus, the presence of confounding factors not registered in the original database, such as differences in SES and comorbidity, could well be an explanation for the different recurrence rates in **study I**, and at the same time constitute major selection criteria for reconstruction: Women employed outside of home and those with a higher education, for example, have a higher probability to undergo IBR than unemployed and retired patients[263,339]. The sensitivity analysis in **study III** substantiated the hypothesis that patients undergoing NSM with IBR represent a selected group of patients with lower comorbidity and a higher SES.

The complexity of **study III** lies in that both lower SES and significant co-morbidities are confounding factors for tumour stage at breast cancer diagnosis as well as for treatment, thus acting as a possible competing cause of death. These factors will therefore affect OS but also BCSS by modulating adjuvant treatments such as chemotherapy and radiotherapy, both of which influence survival[251,263,340]. The persistence of a survival difference between the DIEP flap and control group after adjustments in **study III** suggests either the presence of hitherto unmeasured confounders or a cumulative effect of multiple covariates that may interact in a complex and synergistic ways.

Even though comorbidity was adjusted for in **study III**, the CCI score does not include psychiatric disorders, alcohol and drug abuse, immunosuppressive therapy, bleeding disorders or major surgery, and could thus be too blunt to detect subtler differences between the groups. It could therefore be that a DIEP flap reconstruction is a proxy for better general health,

including comorbidity but also a lower BMI and no smoking habits, which in turn is closely associated to SES, representing another contributing factor to worse survival outcomes.

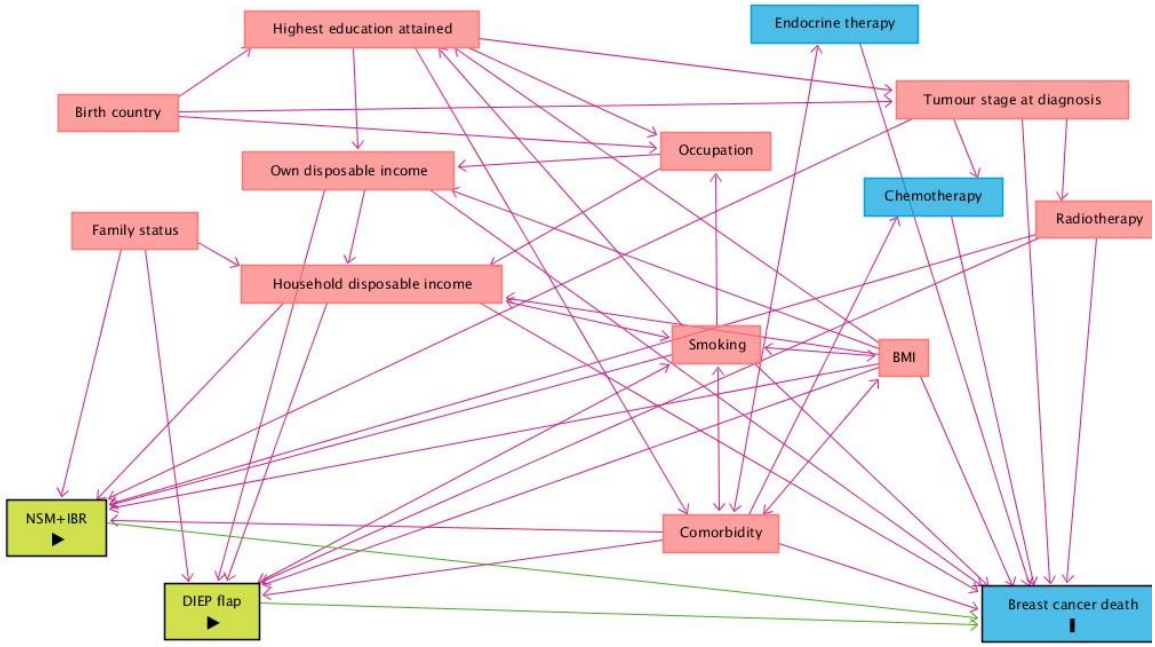


Figure 11. Causal diagram, i.e a directed acyclic graph (DAG) illustrating the interrelations of socioeconomic factors, comorbidity, tumour stage and treatment modalities with the exposures nipple-sparing mastectomy (NSM) with implant-based immediate breast reconstruction (IBR) and deep inferior epigastric perforator (DIEP) flap breast reconstruction and the outcome breast cancer death. Green boxes represent exposures, blue boxes represents the outcome or the mediators of outcome and red boxes represent confounding factors. Green arrows represent causal paths and red arrows represent biasing paths. Created through DAGitty v3.0.

In conclusion, this thesis shows that both NSM with implant-based IBR and delayed DIEP reconstruction can be considered oncological safe procedures with no adverse effect on cancer-specific outcome. Patients opting for breast reconstruction represent a more privileged subset of women in terms of SES and comorbidity; still, differences in OS persisted after adjustment for these factors, most possibly due to selection mechanisms. Although the oncological safety of these procedures is thus suggested, there are other adverse effects to consider in the reconstructive setting, one of which is the effects of radiotherapy on IBR.

5.2 RADIOTHERAPY AND BREAST RECONSTRUCTION

Women in the prior RT group in **study IV** had the highest incidence of IBR failure and reported the lowest scores on four out of five BREAST-Q subscales. Previous studies have reported results in line with our findings, suggesting that prior RT is an independent risk factor for IBR failure regardless of surgical technique[341] and that women with prior RT have a significantly lower quality of life than those receiving postoperative RT or those without any RT[342]. It is important to consider the reasons for prior RT: a majority of such patients have undergone previous breast surgery for breast cancer, and thus undergo their mastectomy due to breast cancer recurrence. This increases surgical risks, but also points at a different severity of the disease and should be suspected to have a negative influence on BREAST-Q scores.

Long-term consequences of breast reconstruction on physical and psychosocial well-being are essential to investigate in order to take the patients' perspective into account. Although RT is associated with adverse effects, a study investigating patients undergoing bilateral implant reconstruction with unilateral irradiation did not show any significant differences in patient satisfaction despite higher complication rates in the irradiated breast[343]. A study by our group showed higher rates for IBR failure in patients with RT, but also that a majority of those without failure would again choose to undergo reconstruction and encourage other patients to do so[175]. Some authors state that the adverse effects of radiotherapy should be met with autologous breast reconstruction and that patients undergoing autologous reconstruction generally report higher cosmetic satisfaction when compared with implant-based reconstruction[167,300]. It is often argued that satisfaction with IBR deteriorates over time, but our results could not support that. It is, however, important to consider that IBR failure is more common in irradiated patients, and a larger proportion of irradiated than unirradiated patients was therefore lost in PRO analyses. Consequently, women suffering IBR failure or choosing to convert to autologous breast reconstructions are those likely to experience declining satisfaction over time, leaving only the most satisfied women in the PRO analysis. In conclusion, although the adverse effects of RT on IBR were again confirmed, the satisfaction of those patients who do not suffer IBR failure or choose to convert to autologous reconstruction does not deteriorate over a long follow-up period.

5.3 STRENGTHS AND LIMITATIONS

One of the main strengths of **studies I-III** is the population-based matched cohort design, reducing the confounding of non-randomized investigations and providing a relatively high level of evidence. The strict matching procedure adjusted for patient and tumor characteristics, aiming at gaining as much similarity to a randomized control trial as possible, since a randomized design would not be ethically feasible in a reconstructive setting today.

Study I is to our knowledge the first matched cohort study comparing NSM and IBR with conventional mastectomy, providing evidence that NSM can be considered an oncological safe procedure in selected cases with a negative retroareolar biopsy. However, the study included a limited study group, and follow-up time was rather short, making firm conclusions hard to draw.

In **studies I-II**, the matching procedure can be regarded as successful since the matching criteria did not differ between both groups. All studies were based on data collected from well-maintained registers, and all patients underwent surgery in Stockholm, hence eliminating geographical variations in selection criteria and even standards of treatment. Furthermore, data on tumour characteristics, treatment, recurrence and death were verified by individual review of medical charts for all studies included in this thesis.

In **study III**, the matching procedure did not account for patients undergoing IBR since the matching was primarily designed for **study II** where IBR was expected not to affect survival in accordance with published evidence. Another limitation in **studies II-III** is the low coverage of important confounding factors such as BMI and smoking habits in the control group. With consideration of the retrospective nature of the study, this missingness could not be adjusted for, and these variables could therefore not be further analysed.

One main strength of **study IV** is the long follow-up time, allowing for a long-term evaluation of both IBR failure and PROs. Detailed clinical data were obtained from medical charts leading to low missingness on tumour characteristics and detailed data on IBR failure, complications and reoperations. One of the main limitations in **study IV** is that patients with IBR failure could not report PROs since the BREAST-Q modules used in this study is impossible to be completed by women who have converted their implant reconstruction to an autologous reconstruction or have had their implant removed.

5.4 METHODOLOGICAL CONSIDERATIONS

5.4.1 Biases

5.4.1.1 Indication bias

Indication bias, or confounding by indication, defines a covariate caused by the indication for the exposure but also known to affect the outcome (i.e. smoking, comorbidity, BMI), thereby modifying an association between the exposure and the outcome. Indication bias is a crucial factor in the setting of **studies II-III** as patients receiving a delayed DIEP flap reconstruction represent a specific subset of breast cancer patients, confounded by indication of the procedure. As a majority of breast cancer recurrences are most likely to occur within the first two years after index surgery[79,192,207], patients at Karolinska University hospital commonly receive a DIEP flap reconstruction earliest 24 months after mastectomy. This creates a 'security margin' between mastectomy and DIEP flap reconstruction which we tried to compensate for by only allowing controls without any recurrence during the corresponding time interval. The metastasis screening undertaken in all patients undergoing DIEP flap reconstruction, however, could further have biased the survival analysis, since the control group may have included patients whose recurrence would have been detected by such screening but was thus left undetected at the time of study inclusion. This may have contributed to the superior survival outcomes after DIEP flap reconstruction.

5.4.1.2 Selection bias

Selection bias implies that study participants may differ systematically from the population of interest. For example, patients included in the NSM or DIEP groups may be healthier, more well-informed, and more often non-smokers with a lower BMI than the general population, thereby not representing all breast cancer patients. Selection bias can arise because groups of participants may be different in other ways than the exposure, leading to the results being biased by confounding.

Since the aim of **studies I-III** was to study the reconstructive groups specifically, no inferences were drawn on the overall population of breast cancer patients but control groups of patients undergoing conventional mastectomy were used for comparison. Interestingly, a subset of patients in the control group as well as in the DIEP group had also undergone IBR in **study II-III**, which, if anything, would have mitigated the observed effects since IBR patients were found to be as selected a group as DIEP patients.

One potential selection bias in **study IV** is that patients choosing to respond to both BREAST-Q questionnaires (i.e. 2012 and 2020) are patients satisfied with the reconstructive results, and that the most dissatisfied patients had either undergone implant removal or autologous reconstruction, or declined to participate in the second survey, thereby filtering out the least satisfied cases. Recall bias, i.e. systematic error due to lack of completeness or accuracy to recall past events or experiences, for example HRQoL at the time of IBR, was limited in this study as the main focus was to investigate the patient-reported outcomes at the moment when the questionnaire was being filled out. Since follow-up times were similar in all groups, and varied within groups, recall bias should be equally affecting all studied groups.

5.4.1.3 Immortal time bias

"Immortal time" refers to the time during follow-up time in which the study participants cannot experience the outcome at question. In **studies II-III**, the follow-up time was calculated both from the time of primary mastectomy as well as from the date of DIEP flap reconstruction or the assigned corresponding time point in control patients. Only the timescale including date of DIEP or index date was, however, included in the survival analysis in order to minimize the risk of immortal time bias.

Because the DIEP group was required to be alive and event-free between mastectomy and the DIEP flap reconstruction, they are during this time considered "immortal" and contributed to "immortal time" to the DIEP group by design. If misclassified or excluded only in the exposure group, the immortal time could lead to biased associations conferring to advantages in survival to the DIEP group. The control group, however, fulfilled the same requirements of "immortality" during the matched time interval.

5.4.1.4 Non-response bias

Non-responder bias occurs due to meaningful differences between responders and non-responders. This bias has been described to convey serious concern in survey studies as it may implicate that patient not responding may differ from those who do, both in aspects of exposure and outcome. If unaccounted for, this could lead to mistakenly estimating population characteristics based on the underrepresentation of some aspects due to non-response. Since previous questionnaire-based studies have reported lower response rates in groups with lower SES [344], a non-responder analysis was undertaken in study IV. This confirmed that the no significant differences were seen between the groups, thereby reducing the non-response bias.

5.4.1.5 Lead-time bias

Lead time is the period between the detection of a disease and its clinical manifestation, which may be affected by e.g. mammography screening. Lead-time bias hence refers to the phenomenon where the early detection of a disease falsely implicates longer survival periods. This attribute is frequently discussed in the context of screening, but also in the context of socioeconomic factors affecting time of diagnosis.

In our studies, the modality of breast cancer detection was not taken into account, but instead, tumour stage was matched for (**studies I-III**). All patients included in **studies I-III** were citizens of Stockholm, where attendance at mammography screening is high[345]. Differences in survival rates between the groups should thus not be due to lead-time bias attributed to differences in attendance to mammography screening. In all studies, the median patient age was within the mammography screening age range. Nevertheless, high screening attendance is more common to patients of higher SES and lower comorbidity, leading to potential differences in detection rate based on these differences.

5.4.2 Internal and external validity

In order to draw valid conclusions for an entire population based on a study sample, it is crucial to assess internal and external validity. Internal validity refers to that conclusion are valid and free from biases for the study sample only, whereas external validity regards validity for the entire population from which the sample is drawn. External validity hence refers to the generalizability of the study sample to the entire clinical population. Internal validity can be affected by either random or systematic errors such as confounding, selection bias or measurement error. While systematic errors are not affected by sample size, random error decreases with larger sample sizes, leading to narrower confidence intervals and hence more precise estimates. In order to obtain both precise and valid estimates, systematic errors need to be accounted for.

For this thesis, information was obtained from nationwide registers with high coverage and validity, and all patients were operated at either the same hospital (Karolinska University Hospital, **studies I-III**) or within the same region. These factors increase the internal validity and with the adjustment for confounding factors, the chance of external validity was increased.

6 ETHICAL CONSIDERATIONS

In our research group, discussions regarding ethical concerns are constantly alive. Prior to every planned study, pros and cons will be weighed against each other and further analyzed for possible harm versus benefit for included patients. This research project is of substantial significance in the field and may contribute valuable information to the ongoing debate concerning the oncological safety following immediate and delayed breast reconstruction. It is therefore of clinical importance that the studies were conducted.

All studies were approved by the Ethics Committee at Karolinska Institutet in Stockholm. Some data were requested from the Regional Cancer Centre (RCC), Statistics Sweden and The National Board of Health and Welfare, while others were obtained by reviewing patients' medical records. These data are sensitive data including information on health, socioeconomic index, educational and occupational level along with individual and household disposable income. Data were therefore de-identified by Statistics Sweden and The National Board of Health and Welfare before delivery.

The use of questionnaires in order to investigate patient-reported outcomes might be uncomfortable for some patients since this might bring back feelings of anxiety associated with the own breast cancer diagnosis. A letter was included with the survey explaining the project and underlining the fact that participation is voluntary. It was carefully assured that the survey was only sent out to patients still alive in order to not upset remaining family members. Ethical dilemmas in this study could include that the personal information extracted from medical charts is obtained without the patient individually consenting to this procedure, which can be seen as a violation of personal integrity. Therefore, the chiefs of departments at all involved hospitals signed a certificate on behalf of their patients, allowing researchers to review medical records. The presentation of the results includes information on an anonymous group level and statistical findings, making personal identification of individuals impossible. After thorough analysis, we conclude that the clinical advantage obtained from the results of the undergone and planned investigations outweighs any potential individual harm.

7 CONCLUSIONS

I. Nipple-sparing mastectomy in the context of immediate implant-based breast reconstruction in selected breast cancer patients does not negatively impact on oncological safety.

II. Delayed DIEP flap reconstruction does not increase the risk of breast cancer recurrence or death.

III. Women with a delayed DIEP flap reconstruction belong to a selected group of higher socioeconomic status and better health than women undergoing mastectomy without any delayed reconstruction, which could explain higher survival estimates in DIEP patients.

IV. Prior and postoperative irradiation increases the risk of reconstructive failure and negatively affects patient-reported outcomes, but effects over time are moderate. Previously irradiated patients should be strongly recommended to consider autologous reconstruction instead of implant-based options.

8 FUTURE ASPECTS

While this thesis sheds light on some important research questions regarding the safety of two common reconstructive methods, many more questions remain unanswered, some of which are outlined below.

Patient satisfaction and quality of life are gaining increasing attention, and by involving patients in the decision-making process leading up to a reconstruction, a higher patient satisfaction should be achievable. Since our data stem from retrospective data collection and thus gather PROs at non-standardized time points, it would be of interest to prospectively register data on breast cancer patients specifically looking at long-term complications, satisfaction and quality of life after breast reconstruction. Since the BREAST-Q questionnaire is not applicable for patients suffering reconstructive failure, such data collection should include further questionnaires not depending on the reconstructive outcome. Such a prospective PRO registration is now underway by a nationwide initiative of the Regional Cancer Centers.

One important subject for future research associated with **studies I** and **II** is the potential influence of postoperative complications on oncological outcomes. Breast cancer reactivation may be initiated through new mutations and scattering of secondary micrometastases, but also through increased levels of growth factors as seen in postoperative complications. Breast reconstruction is associated with a higher risk of postoperative complications than conventional mastectomy, and an important issue to investigate is therefore whether postoperative complications increase the risk of recurrence in patients undergoing implant-based IBR or DIEP reconstruction.

9 SAMMANFATTNING PÅ SVENSKA

I samband med bröstcancerkirurgi kan bröstrekonstruktion genomföras antingen i samma seans, så kallad omedelbar eller primär rekonstruktion (immediate breast reconstruction, IBR) eller i en andra seans, så kallad sen eller sekundär rekonstruktion. Målsättningen med denna avhandling var att studera den onkologiska säkerheten för en allt vanligare metod av implantat-baserad IBR där bröstvårta samt vårtgård sparas (mamill-sparande mastektomi eller nipple-sparing mastectomy, NSM) respektive sekundär rekonstruktion med kroppsegen hud och fettvävnad från buken, så kallad Deep Inferior Epigastric Perforator (DIEP) lambå. Vidare ämnade vi studera skillnader i socioekonomi och samsjuklighet bland patienter som genomgår en DIEP rekonstruktion jämfört med en matchad kontrollgrupp. Slutligen var en av målsättningarna att studera de långsiktiga effekterna av strålning på implantat-baserad IBR genom att undersöka riskfaktorer till protesförlust, samt att evaluera patientrapporterade utfallsmått.

I **studie I** inkluderades samtliga kvinnor som genomgått NSM på Karolinska Universitetssjukhuset 2000-2012. Gruppen matchades till en kontrollgrupp bestående av bröstcancerpatienter som hade genomgått mastektomi utan efterföljande primär rekonstruktion. Totalt inkluderades 69 fall och 206 kontroller. Inga lokalrecidiv registrerades i studiegruppen jämfört med sju stycken i kontrollgruppen (P=0.197), och inga signifikanta skillnader i överlevnad kunde identifieras.

I **studie II-III** inkluderades samtliga patienter som hade genomgått en sekundär rekonstruktion med DIEP lambå vid Karolinska Universitetssjukhuset 1999-2013 (254 DIEP fall) samt en kontrollgrupp av bröstcancerpatienter som hade genomgått mastektomi utan sekundär rekonstruktion (729 kontroller). I **studie II** ämnade vi att studera risken för bröstcancerrecidiv samt bröstcancer-specifik överlevnad (BCSS). Bröstcancerrecidiv var vanligare i kontrollgruppen (23.9 %) än i DIEP-gruppen (19.7 %, P=0.171). Efter justering för tumörfaktorer samt behandling var den totala femårs-överlevnaden (HR 1.91, 95 % CI 1.22–2.98), men inte den bröstcancer-specifika (HR 1.35, 95 % CI 0.80-2.26), signifikant lägre i kontrollgruppen än i DIEP-gruppen. I **studie III** ämnade vi att undersöka huruvida dessa överlevnadsskillnader påverkats av socioekonomiska faktorer och samsjuklighet. I gruppen som genomgick DIEP rekonstruktion var det oftare förekommande att fortsätta utbildningen efter grundskolan, att ha en högre inkomst och att befinna sig i en relation, samt att ha en lägre samsjuklighet enligt Charlson Comorbidity Index. Efter justering för dessa faktorer var den totala överlevnaden fortsatt signifikant bättre för patienter som genomgått rekonstruktion med DIEP lambå.

I **studie IV** inkluderades samtliga bröstcancerpatienter som genomgått implantat-baserad IBR vid något av de fyra Stockholmssjukhusen 2007-2011 (754 fall). Dessa hade redan undersökts 2012 med enkäten BREAST-Q, som studerar fysiskt och psykiskt välmående samt nöjdhet med rekonstruktionen. Kohorten delades in i tre strålbehandlingsgrupper: 386 fall som inte erhållit strålbehandling (radiotherapy, RT), 64 som hade erhållit RT innan IBR samt 304 fall som erhållit RT efter IBR. Primärt utfallsmått var implantatförlust, definierat som borttagning av protes med eller utan samtidig eller senare bröstrekonstruktion med kroppsegen vävnad. Totalt 128 fall (17 %) av protesförlust registrerades: 8.8 % i den icke strålade gruppen, 31.3 % i den tidigare strålade gruppen och 24.3 % i gruppen som erhållit postoperativ RT. Riskfaktorer för implantatförlust var RT, ålder >50 år vid tidpunkten för IBR, BMI > 25, och postoperativa kirurgiska komplikationer.

BREAST-Q enkäten skickades till samtliga patienter i livet som inte nått det primära utfallsmåttet. Svarsfrekvensen var 72.2 %. Kvinnor som tidigare erhållit RT skattade lägst i jämförelse med de andra två grupperna på de flesta skalor av enkäten. Kvinnor som erhållit postoperativ RT skattade signifikant lägre endast på skalan för fysiskt välmående. Longitudinella jämförelser mellan undersökningen år 2012 och 2020 visade att skattningarna på skalan för psykosocialt välmående hade ökat bland kvinnorna som erhållit postoperativ RT. De icke strålade kvinnorna rapporterade lägre nöjdhet än tidigare avseende brösten samt avseende det övergripande resultatet av bröstrekonstruktionen.

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